NATIONAL CANCER INSTITUTE
EARLY THERAPEUTICS CLINICAL TRIALS NETWORK
PROGRAM GUIDELINES

DIVISION OF CANCER TREATMENT AND DIAGNOSIS
NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH

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Part 1: Overview of the ET-CTN

1.I. Introduction

1.I.1. Purpose and Content of Guidelines

Guidelines for the National Cancer Institute (NCI) Early Therapeutics Clinical Trials Network (ET-CTN) have been developed by staff of the Division of Cancer Treatment and Diagnosis (DCTD), NCI, in consultation with staff of the Office of Grants Administration (OGA) and the Division of Extramural Activities (DEA), NCI, as well as with the advice of qualified members of the extramural scientific community. The purpose is to describe the NCI's goals and expectations for the various applicants and investigators, peer reviewers, and the National Institutes of Health (NIH) staff who are involved with this Program. They are intended to encourage an innovative state-of-the-art early therapeutics clinical trials program executed by an integrated network of investigators and participating institutions who are experienced in conducting early phase clinical trials with emphasis on molecular characterization, biomarker assays, pharmacogenomics, integral and integrated assay development, pharmacodynamics (PD), pharmacokinetics (PK), and advanced imaging technology.

The guidelines describe how the NCI envisions transformation of the NCI-sponsored cooperative experimental therapeutics clinical trials program from a series of separate organizations conducting early phase cancer treatment trials into a consolidated, integrated NCI Experimental Therapeutics-Clinical Trials Network (ET-CTN). The ET-CTN is complementary to the seven phase 2 contracts and the National Clinical Trials Network (NCTN) that focus on late phase development with an emphasis on phase 3, disease-specific studies. The ultimate purpose of the ET-CTN is to define approaches to cancer treatment based on molecular characterization and biomarker assay development used for patient selection in early phase experimental therapeutic clinical trials. Participants, in conjunction with NCI staff, will collaborate cooperatively to achieve ET-CTN objectives. NCI will provide centralized support for approved, early phase trials. This support will cover such activities as data management, clinical trial registration, regulatory support, and Central Institutional Review Board (CIRB) review for approved, early phase trials.

This Guidelines document is divided into four parts as described below:

A. **Part 1 – Overview of the ET-CTN Program**
   This part describes the ET-CTN and its policies and procedures, including the Terms and Conditions of Award.
B. **Part 2 – Guidelines for Submission of Competing Applications and Description of the Review Process**
   This part describes the pre-application consultation, application submission instructions, and peer review processes for competing applications.
C. **Part 3 – Guidelines for Submission of Continuing Applications**
   This part describes the progress report and budgetary issues for non-competing continuation applications.
D. **Part 4 – Appendices**
   This part contains appendices relevant to the policies and procedures associated with the ET-CTN and with the application and review processes.

A variety of rules and regulations affect the ET-CTN (e.g., NIH Grants Policy, policies of the Office of Human Research Protections, etc.). These Guidelines are intended to cover NCI/DCTD's general and

special requirements for the ET-CTN and to supplement NIH and DHHS policies. These Guidelines, as well as the policies of all awardees under the ET-CTN, must adhere to NCI, NIH, and DHHS policies. Applicants should contact the responsible NCI ET-CTN Director and the NCI/DCTD ET-CTN Senior Program Specialist in order to resolve any apparent discrepancies in the interpretation of these Guidelines and/or if they believe these Guidelines conflict with other applicable federal policies.

NCI ET-CTN Director: Dr. S. Percy Ivy
Phone: 301-496-1196
Email: ivyp@mail.nih.gov

NCI/DCTD ET-CTN Senior Program Specialist: Mrs. Kim Witherspoon
Phone: 301-496-8866
Email: kw265c@nih.gov

1.I.2. Background, Overview, and Purpose of the ET-CTN

The NCI supports a program to facilitate the early stages of development of cancer therapeutics. The early therapeutics development program funds and oversees clinical development of new agents for the Cancer Therapy Evaluation Program (CTEP).The program has contributed to the clinical development of many anticancer agents. The early therapeutics development program has rapidly taken advantage of new scientific opportunities to promote therapeutic innovation that is generally not addressed by the private sector. The program has:

1. Utilized new discoveries regarding signaling pathways that promote tumor growth and metastases, as well as those that are multiple, redundant, and induced when a "dominant pathway" is inhibited to develop novel therapies.
2. Sponsored approximately 200 investigational agent combination clinical trials (147 since 2001). These combinations include 41 new molecular entity (NME)/NME combinations.
3. Used new technologies to allow rapid, deep assessment of DNA mutations, methylation patterns, gene expression profiles and RNA expression arrays in human tumor samples.
4. Conducted studies with genetically defined tumor subtypes to optimize potential benefit to patients and to facilitate characterization of drug effect on the putative target.
5. Defined dosing and dose modification licensing recommendations for patients with hepatic and renal dysfunction.
6. Evaluated drug/drug interactions in patients with HIV-associated malignancies receiving Highly Active Antiretroviral Therapy (HAART).

This program has been designed and implemented to ensure that: (1) early phase clinical trial designs can accommodate new therapeutic approaches; (2) early phase clinical trials are conducted safely and efficiently; and (3) potential doses and schedules are determined for use in patients in clinical trials to evaluate agent combinations and/or for Phase 2 testing. As of September 2012, NCI currently sponsors 85 early phase clinical trials with novel agent combinations, most initiated during the last several years. Approximately two-thirds of the Phase 1 combination studies listed in ClinicalTrials.gov and in published literature have been conducted in the NCI Phase 1 program, which performs only cancer-relevant studies.

The NCI promotes exploration of scientifically important clinically-relevant questions in areas that: (1) are not the primary focus of pharmaceutical companies; (2) involve investigational agent combination studies; (3) are aimed at maximizing target inhibition; (4) are aimed at abrogating signaling through parallel and complementary pathways in cancer cells; and (5) molecularly characterize patients' tumors

to further elucidate mechanisms of therapeutic response and/or resistance. NCI's strategy includes development and assessment of biomarkers for patient selection, and identification of putative predictive and prognostic markers.

Through NCI's experimental therapeutics program, 540 Investigational New Drug Applications (INDs) for investigational agents have been filed since 1972. CTEP currently holds approximately 100 INDs for investigational oncology agents which involve 60 pharmaceutical/biotechnology collaborators. CTEP prepares and submits approximately 8-15 IND applications to the Food and Drug Administration (FDA) each year. Agents under evaluation include small molecules, antibodies, vaccines, targeted toxins, oligonucleotides, and gene transfer agents.

In recent years, there have been unprecedented increases in the accumulation of data on mutations, epigenetic changes, and other "-omics" aspects with potential significance for various oncogenic molecular pathways. This new information has led to the realization that assessing various cancer-relevant molecular abnormalities is essential for optimal and efficient development of targeted agents designed to exploit specific abnormalities in the therapeutic context. Combination studies with molecularly targeted agents have become an increasingly high priority for NCI, based upon evidence that resistance to initially effective single agents often develops quite rapidly in many adult tumors.

The purpose of this Funding Opportunity Announcement (FOA) is to transform the NCI-sponsored cooperative experimental therapeutics clinical trials program from a series of separate organizations conducting early phase cancer treatment trials into a consolidated, integrated NCI ET-CTN. This FOA will support up to 10 ET-CTN sites dedicated to new agent developmental efforts with emphasis on early phase clinical trials. ET-CTN awards will provide the major resource for rapid, efficient, systematic evaluation and determination of optimal dose/schedule for specific agents and combinations of investigational agents sponsored under CTEP INDs. Members of the ET-CTN will work on investigational agent-specific trans-network project teams to define the drug development plan, and conduct experimental therapeutic clinical trials for agents with INDs held by the NCI DCTD, CTEP (http://ctep.cancer.gov/). Activities designed to assess target engagement will be expected.ET-CTN sites will be expected to extensively characterize patients' tumors on a molecular level to select appropriate patients for specific treatments, and to explore mechanisms of resistance and response to assist in defining follow-on treatment or determine future combination therapies.

1.II. Goals and Organizational Structure for the NCI Early Therapeutics Clinical Trials Network (ET-CTN)

1.II.1. Goals of ET-CTN Research

1.II.1.A. Experimental Therapeutics Program with Phase 1 Emphasis

The clinical research focus of the ET-CTN is early therapeutics with an emphasis on early phase experimental therapeutics studies. Many of the agents in the NCI portfolio are novel, molecularly targeted agents that undergo more complex development than conventional chemotherapeutic agents or include development and assessment of biomarker assays for patient selection and identification of putative predictive and prognostic markers. The development and evaluation of integral and integrated biomarkers are essential to select individuals for targeted treatment. PD assessment of drug effects on molecular targets requires expertise in assay development, molecular imaging capabilities, tumor and specimen acquisition and handling, and genomic and expression array analysis. Evaluating tumor specimens at baseline and at the time of progression to define response and resistance mechanisms, including co-opted and compensatory pathway activation, will assist in the identification of follow-on

therapy and appropriate investigational combination treatment regimens. These investigations provide the foundation for therapeutics development through an enhanced understanding of human, functional cancer biology.

The Goals of the ET-CTN include:

1. Evaluation of innovative cancer treatments consistent with national priorities for developmental therapeutics clinical cancer research using a coordinated, collaborative, and inclusive team-based approach for generating ideas for early phase experimental therapeutic clinical trials.
2. Prioritization of clinical trials that are designed to answer important questions relevant to the development of specific agents, as well as assuring that the trials are not duplicative of research funded by industry or other sources.
3. Efficient and timely activation and conduct of clinical trials meeting all regulatory requirements.
4. Effective integration of preclinical findings into ET-CTN trials along with acquisition of human samples for correlative laboratory studies.
5. Collaboration among institutions and investigators with expertise in various medical specialties and research areas (e.g., molecular characterization, pharmacology, cancer biology, clinical oncology, imaging) relevant to treatment of cancers in adults.
6. Enhanced emphasis on education and training of young investigators.

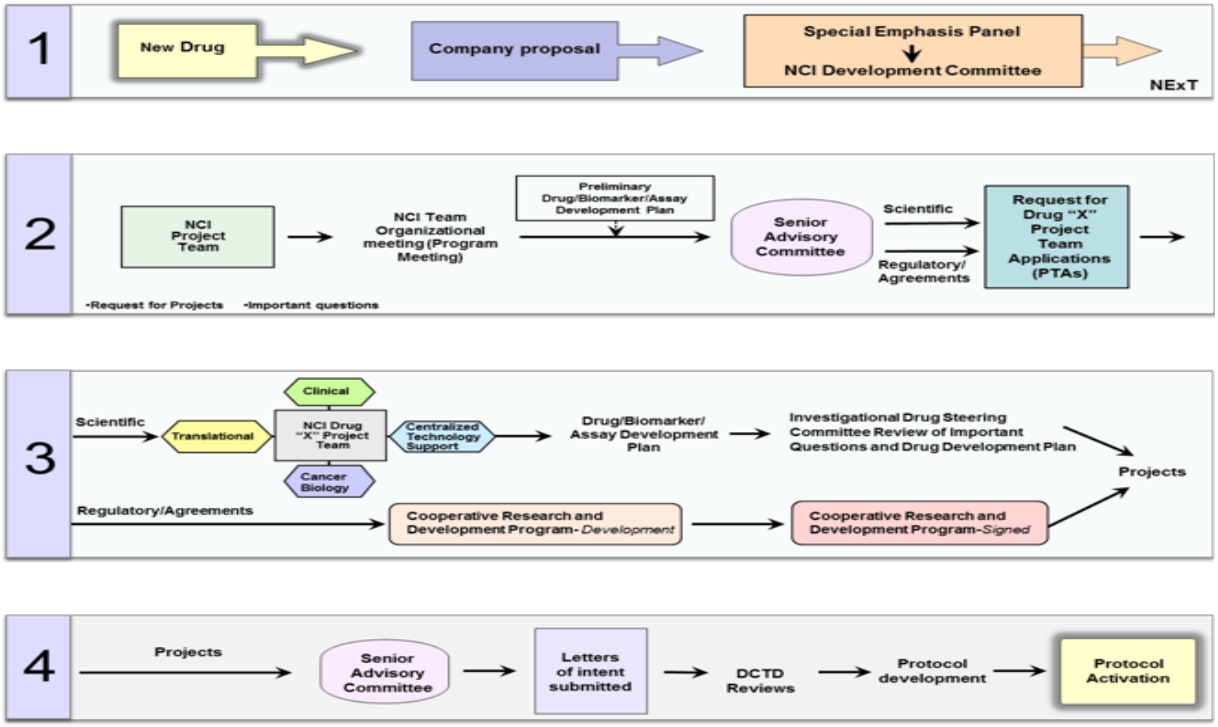
The experimental therapeutics program uses the specialized expertise of academic centers and allows CTEP to create collaborations to leverage development of a particular agent or agent combinations. Combination studies with molecularly targeted agents have become an increasingly high priority for NCI, based on the clinical relevance of these agents and lack of single-agent, long-term effectiveness. Because of its extensive collaborations with industry and the research community, NCI is uniquely positioned to facilitate important studies which often involve combining agents from different pharmaceutical companies and are often challenging to accomplish in the private sector. The majority of agents are from pharmaceutical and bio-pharmaceutical collaborators, but some may come from academia.

The ET-CTN is designed to accomplish its objectives by forming multi-institutional, multi-disciplinary Project Teams, which will define early drug development clinical trials of novel drugs and/or combination therapies. All ET-CTN awardees will be expected to participate on Project Teams to define the development plans for specific novel agents/combinations relevant to their expertise and capabilities. Representatives of other NCI-supported programs will also participate on those teams. The NCI will coordinate and support logistically the formation and operation of the Project Teams. As novel agents progress from Phase 1 to Phase 2 clinical trials, investigators representing various relevant NCI-supported programs will collaborate with NCI's Investigational Drug Steering Committee (IDSC) and its disease-specific steering committees. These Project Teams will develop novel treatments requiring molecularly guided patient selection and pathway-driven investigational combination therapies in a wide variety of malignancies.

Investigators at ET-CTN participating institutions may submit research project proposals as part of the Project Teams. Additionally, Investigators may respond by submitting Project Team Applications (PTA) for trials and a Letter of Intent (LOI) proposing clinical trials in response to requests from CTEP. Unsolicited LOIs for proposals for clinical trials will be considered. Information regarding the submission of LOIs may be found at: http://ctep.cancer.gov/protocolDevelopment/letter_of_intent.htm.

A schematic of the development cycle for early therapeutics is outlined below:

Development Cycle for Early Experimental Therapeutics



Overview of the Coordination of the Experimental Therapeutics Clinical Trials Network

To address the new opportunities and challenges in the development of novel targeted cancer therapeutics, the NCI has established a systematic approach with several interacting functional components. The NCI Experimental Therapeutics Program (NExT) is the portal through which NCI brings investigational agents into DCTD/CTEP for development. After a new agent is chosen for development, the Investigational Drug Branch (IDB) Project Team Leader will form an NCI Project Team from the various clinical, translational, and basic biology programs at NCI. Members of the Project Team will draft a preliminary drug/biomarker/assay development plan. Once this plan is reviewed and approved by the NCI Senior Advisory Committee (SAC), part of the NeXT approval process, NCI will send out a request for PTAs to the ET-CTN members, awardees of the NCI Phase 2 Contracts Program, NCTN awardees, and other appropriate investigators. The request for PTAs will include publically available information about the drug being developed and the types and focus of the clinical trials being considered in the preliminary drug/biomarker/assay development plan. Once the PTAs have been reviewed and prioritized by NCI, the IDB Project Team Leader will constitute the Drug "X" Project Team with the Program Director(s) (PDs)/PIs Lead Protocol Organization (LPOs) of the PTAs that have been approved as well as other relevant subject matter experts. This Drug "X" Project Team will be charged with refining the drug/biomarker/assay development plan for a team presentation to the IDSC. Following IDSC evaluation, the drug/biomarker/assay development plan will be finalized by the IDB and Letters of Intent (LOIs) will be requested from the Drug "X" project team. After approval of the LOIs by CTEP/DCTD, the protocols will be developed and submitted to DCTD/CTEP for final approval before activation.

1.II.1.B. Ancillary Studies

The database of patient information accumulated in the course of ET-CTN clinical trials, the systematic large-scale collection of biospecimens from those trials, and the opportunity to correlate specific features of those biospecimens with patient outcome, provide the Network with unique opportunities to address scientific questions about molecular genetics, epidemiology, pathology, and other cancer-related topics. Such investigations can add considerable strength to a Network's total scientific program and are encouraged. A variety of funding mechanisms may be applicable for supporting ancillary studies.

1.II.1.C. Collaborations Among Network Partners and External Investigators

ET-CTN participating institutions are encouraged to collaborate with each other and with other NCI-funded programs and investigators (e.g., NCI Cancer Centers, Specialized Programs of Research Excellence [SPOREs], early clinical trials networks, other NCI-supported multi-site clinical trials networks, and R01 and P01 investigators). These collaborations may include advancing research ideas from early phase studies to phase 3 trials (with hand-offs between various NCI-funded programs where appropriate), providing correlative science services for large, multi-site studies, and participation in multi-site trials conducted throughout the NCI-supported clinical trials system. Collaborations with ET-CTN Lead Academic Organization (LAO)/LPO are encouraged, as is the collaboration with investigators outside the ET-CTN.

1.II.1.D. Conduct of ET-CTN Clinical Research

Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and the human subjects who participate in research studies. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Participating institutions in the ET-CTN should strive to comply with this standard to the greatest degree possible since it provides public assurance that the rights, safety, and well-being of trial patients are protected, and that the clinical trial data are credible. Information on GCP standards in FDA-regulated clinical trials is provided at: http://www.fda.gov/oc/gcp/default.htm.

The integrity of clinical data is a function of the entire process of data recording, data collection, reporting, and analysis. ET-CTN participating institutions must follow detailed Quality Control (QC) and Quality Assurance (QA) plans and systems to assure protocol adherence in the administration of protocol-prescribed therapy and in the uniform collection of data. Vigilance to detect honest errors, whether systematic or random, as well as data falsification, is especially important to clinical trials since independent replication of most trials is not feasible.

Scope of Scientific Activities

Consistent with the objectives and priorities of the ET-CTN, each proposed ET-CTN site and its investigators need to be capable of clinical research involving the following main scientific activities:

1. Conducting early phase experimental therapeutic clinical trials (pilot, phase 0, phase 1, and/or specific small or randomized phase 2 clinical trials) using single or combinations of novel agents from the NCI CTEP IND portfolio. The emphasis will be on novel agents that target relevant cancer cell signaling pathways and essential cellular machinery involved in the regulation of angiogenesis, cell survival, apoptosis, proliferation, and differentiation.
2. Participating on investigational agent-specific Project Teams to define the drug development plan.
3. Assessing PK and PD of the studied agents and establishing relationships between the dose, schedule, exposure, and effect.

4. Developing statistically appropriate clinical trial designs, including integral and integrated biomarker trials, accelerated titration, Bayesian design, and other advanced design schemes.
5. Studying special populations, including investigations involving patients with hepatic and/or renal dysfunction(s).
6. Establishing safe and biologically active treatment schedules for patients with cancer.
7. Obtaining mechanistic proof-of-principle data for new agents directed at novel molecular cancer targets.
8. Collecting, processing, and, when appropriate, storing biospecimens for biomarker analysis.
9. Evaluating data from clinical trials that involve combinations of CTEP IND agents.
10. Evaluating data from related laboratory studies that assess the nature of drug-drug interactions (additive/synergistic/antagonistic).
11. Evaluating translational endpoints in clinical trials of investigational agents (e.g., the levels of expression and/or activity of molecular targets and/or downstream effectors pertinent to a given agent).

1.II.1.E. Structure of the ET-CTN

The ET-CTN will consist of up to 10 extramural LAOs and one intramural component, the Developmental Therapeutics Clinic, DCTD, NCI. Each LAO will possess an integrated organizational structure with scientific leadership and a site organization that will facilitate team science, PK, PD, biomarkers, clinical trials support, statistics, protocol development, data management and administration, and regulatory and research pharmacy management. The clinical trials of the ET-CTN must be conducted in accordance with the instructions as outlined in the Investigator's Handbook, A Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis, National Cancer Institute (http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf).

The following definitions related to organization structure will be utilized:

1. Lead Academic Organization (LAO): The institution receiving the award under this Cooperative Agreement. In the case of a Multiple Program Director/Principal Investigator (PD/PI) application, the LAO will be the institution of the designated contact PD/PI on the application.
2. Integrated Component: A component of the awardee institution that may be at a different location but is under a shared financial system and governance structure.
3. Affiliated Organization (AO): An institution or academic site collaborating with the LAO. For multiple PD/PI applications, an AO is defined as an academic site(s) led by the designated multiple PIs on the Cooperative Agreement, other than the LAO institution.
4. ET-CTN sites: the LAO, integrated components, and AOs.
5. Lead Protocol Organization (LPO): Institution of the protocol PI.

Applicants responding to this FOA may include single or multiple institutions, as needed, to propose, develop, and perform early clinical trials, and to analyze the results of such trials. Academic participating sites may include NCI Comprehensive and Clinical Cancer Centers, as well as other major U.S. academic cancer centers and other collaborators. The functions of specific required organizational components for each ET-CTN site are outlined below.

Key Capabilities and Attributes of Required Components

For the outlined goals of the ET-CTN, applicants responding to this FOA need to have appropriate capabilities and attributes. These aspects are defined below as key components that are expected to provide a scientific and organizational framework for the ET-CTN.

1.II.1.F. Key Components

Each awarded LAO will have the following primary responsibilities:

1. **Scientific Leadership and Site Organizational Structure**
   The purpose of this component will be to provide scientific leadership for the ET-CTN site, plans for ET-CTN participation, and the organization of the site. It is essential that investigators applying for the ET-CTN awards have considerable expertise and well documented experience and accomplishments (past performance) in the conduct of cancer clinical trials and clinical development of experimental therapeutics. This experience may be acquired through a past performance in the NCI Early Phase Clinical Trials Program with Phase 1 Emphasis. However, previous affiliation with the NCI Early Phase Clinical Trials Program with Phase I Emphasis is NOT required and all qualified applicants are encouraged to apply.

   A. Scientific Leadership:
      i. Program Director(s)/Principal Investigator(s) (PD/ PIs) at the academic participating sites are expected to be national and international leaders in the areas of science and administration. PDs/PIs should have documented administrative leadership experience.
      ii. PDs/PIs at the ET-CTN sites are expected to be national and international leaders in cancer related clinical trials of novel therapeutic agents, related clinical areas, and translational research relevant to such studies.
      iii. PD(s)/PI(s) are expected to accomplish cooperative and productive collaborations between participating ET-CTN sites and other clinical and translational research investigators using a team science approach.
      iv. Scientific Leadership is expected to oversee all clinical trials operations. Each ET-CTN site will be required to establish a specific structure to oversee the conduct of early phase therapeutic clinical trials, ensure data safety monitoring, compliance with the required policies and regulations, and facilitate interactions with other ET-CTN and NCI staff.
      v. Assure timely preparation, presentation, and publication of clinical trial results and research findings at global meetings.

   B. Site Organizational Structure:
      i. Establish a clinical trials operations office to oversee the conduct of early phase therapeutic trials. This office is expected to have the requisite statistical expertise for trial design/monitoring and coordinate patient enrollment on all clinical trials open in the ET-CTN.
      ii. Ensure data safety and monitoring oversight for patients on all active trials.
      iii. Establish an internal committee to monitor and oversee patient safety, protocol compliance, and outcome and response review.
      iv. Ensure collaboration between ET-CTN members and NCI staff to achieve ET-CTN goals and objectives.

2. **Team Science for Project Development**
   Each ET-CTN site will be expected to lead and/or participate in multi-disciplinary scientific Project Teams formed during the development and implementation of ET-CTN drug development plans. This objective requires that ET-CTN investigators are highly capable of inter- and trans-disciplinary team-based research efforts, including potential for interactions with

investigators from other ET-CTN sites, other NCI-sponsored programs, and NCI staff members. This is carried out by:

A. Focusing on early drug development using inter- and trans-disciplinary team-based scientific research project approaches, nationally or internationally.
B. Demonstrating cooperation among investigators across disciplines.
C. Promoting team efforts answering complex research challenges.
D. Demonstrating the ability to enhance existing capabilities and adapt new approaches to reach collaborative team goals.
E. Describing procedures for addressing failure by investigators or institutions to meet study timelines and objectives.
F. Assessing clinical results and defining scientific criteria for subsequent prioritization of agent development.

3. PK/PD, Biomarker Assay, and Molecular Characterization of Patients

Each ET-CTN site must have the capability to support clinical trials by conducting various laboratory testing of clinical specimens as needed. This component will support laboratory testing by:

A. Developing validated assays. Assays used for patient selection, stratification, or determination of treatment must be performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, and may be subject to FDA oversight as an investigational device exemption (21 CFR 812).
B. Using validated molecular imaging capabilities, as appropriate.
C. Coordinating the acquisition, handling, preparation, evaluation, and shipment of specimens to ET-CTN sites or tumor banks/repositories.
D. Analyzing tumor and specimen evaluation capabilities to define response and resistance mechanisms and identify follow-on therapy and investigational combination treatment regimens.
E. Analyzing genomic and expression array data or other biomarker-based studies.
F. Enhancing understanding of human, functional cancer biology.
G. Supporting and overseeing processes for requesting and reviewing proposals to perform PK/PD, and various correlative laboratory studies.
H. Participating in the molecular characterization of all patients enrolled on early phase therapeutics trials. This includes the requisite expertise in acquiring fresh biopsy specimens from a high percentage of patients on trials (even if invasive procedures are required).
I. Ensuring correlation of appropriate molecular, biological, and pharmacological endpoints with clinical outcomes.

4. Coordination of Clinical Trials and Associated Activities

The research and managerial coordination component will be responsible for the organization and coordination for all aspects of clinical trials operations, implementation, and safe conduct. The administrative component shall collaborate with NCI support infrastructure to coordinate ET-CTN activities. The coordination component will be responsible for the organization for all aspects of clinical trials operations, implementation, and safe conduct, including:

A. Facilitating member interactions and communications for single institution or multi-institution sites.

B. Supporting clinical trials performed by the research project team by identifying, recruiting/affiliating, and retaining qualified personnel necessary for the conduct of clinical trials.
C. Collecting and analyzing data by appropriate medical, statistical, and Clinical Research Associate (CRA) staff members.
D. Providing high-quality data management using an effective QA/QC program, including internal review and oversight of data submission.
E. Monitoring activities to guarantee data integrity and ample auditing.
F. Performing statistical evaluations essential for the appropriate design, conduct, and analysis of all clinical trials.
G. Participating in an NCI-sponsored CIRB.
H. Reporting program performance.
I. Distributing funding and reimbursing participating institutions and laboratories for work performed.
J. Reporting and monitoring safety on all trials enrolling patients at their site.

5. Research Pharmacy Management

It is essential that all ET-CTN sites have a dedicated component to conduct investigational drug pharmacy operations required to adequately fulfill obligations related to investigational agents. This component should have:

A. Secured access to storage space and storage unit(s) necessary to meet storage conditions of agent(s).
B. Ability to properly order, receive, store, and maintain investigational agents.
C. Safe and secure handling, preparation, and disposal of dangerous goods, and hazardous and infectious substances.
D. Written standard operating procedures (SOPs) related to investigational agent management.
E. Existing procedures for reconciling deviations.
F. Research pharmacy personnel experienced in the preparation, storage, and dispensing of investigational agents.

6. Career Development and Mentored Training of Junior Investigators

Each ET-CTN site will be expected to organize appropriate career development and mentored training. The program should provide an adequate mentorship and/or training for new and junior investigators, including opportunities for trainees to lead clinical trials and participate in future ET-CTN activities and/or initiatives. The development of junior faculty through mentorship, initiatives, and activities is demonstrated by:

A. Conducting experimental therapeutics education and training for junior investigators (less than 7 years post oncology fellowship training).
B. Mentoring and/or training programs for new and junior investigators.
C. Providing opportunities for young investigators to lead clinical trials, as well as participate in experimental therapeutic development activities and/or initiatives.
D. Providing opportunities to enhance skill in and teach principles of experimental therapeutics.
E. Integrating translational science (bench-to-bedside and bedside-to-bench) into the training/mentoring program.

1.II.1.G. ET-CTN Sites

The PI(s) at the LAOs are expected to accomplish collaboration between all participating ET-CTN sites and other clinical and translational research investigators locally, nationally, and internationally. Network members, sites, or others will be able to enroll patients on all trials conducted by the ET-CTN, irrespective of the LPO leading the trial. All ET-CTN sites will be responsible for screening, enrolling patients, collecting required biospecimens, treating patients, and monitoring and reporting safety information throughout the conduct of their clinical trials.

1.II.1.H. Interactions with Other NCI-supported Programs

The ET-CTN awardees will be expected to interact as appropriate with entities/programs such as the NCI –Supported Specimen Resources, the NCI Cancer Trials Support Unit (CTSU), the Clinical Trials Monitoring Service (CTMS), the NCI CIRB, and NCI Advisory and Scientific Committees including the IDSC.

1. **NCI –Supported Specimen Resources**
   See: http://cdp.cancer.gov/humanSpecimens/finding.htm.
   The advent of powerful molecular technologies and the emergence of targeted therapeutics have opened the door to developing more effective and, in some cases, individualized treatment of patients with cancer aimed at specific cancer-related pathways. Development of effective therapeutic interventions, based on the comprehensive analysis of critical pathways of cancer initiation and progression, requires access to biological specimens from patients treated in prospective randomized trials. High-quality biological specimen banks containing uniformly collected specimens from such trials along with validated clinical and outcome data are essential for development and delivery of new diagnostic and predictive tools to guide the use of targeted therapies.

   The infrastructure needed to ensure the collection of high-quality, well-annotated human specimens from ET-CTN trials is funded and administered by DCTD through the ET-CTN Cooperative Agreement awards. Review of research project requests for use of biospecimens banked from ET-CTN trials is administered by DCTD through the ET-CTN.

   The infrastructure to support banking of the biospecimens collected from ET-CTN trials is funded and administered through a separate U24 Cooperative Agreement award. For more information on this biobanking program see: http://biospecimens.cancer.gov/default.asp. The range of activities that can be covered under the Human Specimen Banking U24 awards includes support and training of staff to collect and ship biological specimens from the collection sites to the central banks, to oversee receipt of specimens, and to process specimens at the central bank, including conducting pathologic review and providing histology services. The funding can cover costs for equipment and supplies, including shipping materials and shipping costs, storage costs (such as liquid nitrogen for freezers), and costs for informatics to track specimens, as well as miscellaneous costs such as travel to required meetings and maintenance contracts and subcontracts to participating institutions. Additional support can be obtained to cover some of the costs associated with review of requests for specimens and data, and retrieval and shipment of specimens to researchers, as well as return of blocks to the collecting institutions for patient care or legal requirements. The costs of organizing or operating data centers beyond those incremental costs directly associated with transmission of data related to operation of the banks are not covered by this funding mechanism.

2. **The Cancer Trials Support Unit (CTSU)**
   The CTSU is a service of NCI's CTEP developed to provide administrative support for the clinical trials conducted by the ET-CTN as well as other NCI-supported clinical trial programs. Key areas in which the CTSU supports the ET-CTN include the following:

   A. Providing 24/7 centralized, web-based, patient enrollment for all ET-CTN trials via the Open Patient Enrollment Network (OPEN) supported by ET-CTN site rosters and institutional review board (IRB) approvals provided via the Regulatory Support System (RSS); and
   B. Providing support for the Common Data Management System (CDMS), including remote data entry, used for all ET-CTN sites and ET-CTN trials, and helping to harmonize procedures and policies related to operational aspects of trial conduct across the ET-CTN.

   More information regarding the CTSU, including other services and new initiatives, is available at: http://www.ctsu.org.

3. **NCI Clinical Trials Monitoring Service (CTMS)**
   To assist CTEP in fulfilling its regulatory responsibilities as an IND sponsor and to assure protocol compliance and source data verification, resources for data management and monitoring will be provided under contract through the CTMS. The benefits of centralized data management include increased efficiency by having a single entity responsible for the study, build a core set of common electronic Case Report Forms (eCRFs) to be utilized via Medidata Rave, data management, QA, adverse event analysis, and study reporting generation, including reporting to the Clinical Trials Reporting Program (CTRP) and clinicaltrials.gov. The specific tasks in the contract pertaining to the ET-CTN include:

   A. **TASK I:** To provide a resource, and patient data QC reviews for DCTD for clinical investigators conducting early phase experimental therapeutic clinical trials conducted through the ET-CTN. All participating institutions must submit data to CTMS using the NCI-procured clinical data management system (CDMS), Medidata Rave, every 2 weeks. The CTMS will provide technical and administrative support for the ET-CTN Data Safety Monitoring for early phase experimental therapeutic studies conducted by the ET-CTN.
   B. **TASK II:** To provide an onsite auditing resource for the DCTD to assure that contractors, grantees and other clinical investigators conducting early phase experimental therapeutic clinical trials are in compliance with federal regulations, GCPs, and NCI policies and procedures in order to verify submitted protocol patient data, and assure the quality of submitted data, protocol compliance, and patient safety through proper reporting.

4. **NCI Central Institutional Review Boards (CIRBs)**
   The NCI CIRB provides a centralized approach to human subject protections that streamlines local IRB review of adult and pediatric national multicenter cancer treatment trials. CIRB membership includes patient advocates, oncology physicians, nurses and other health professionals as well as ethicists. The benefits to research participants include study review by individuals who represent a broad range of oncology expertise, as well as specialized expertise such as pediatric oncology and early drug development. The benefits to investigators include time saved since they can download an already completed IRB application for each study as well as eliminating the need to submit amendments, continuing reviews, and non-local Adverse Events (AEs) to their IRB. In addition, subjects are enrolled in trials faster since the full local IRB does not need to meet. The benefits to the ET-CTN include a cost efficient approach that avoids

duplication of effort at each site. The CIRB provides the services of a fully constituted IRB and provides a comprehensive and efficient mechanism to meet regulatory requirements pertaining to human subject protections including: initial reviews, continuing reviews, review of amendments, and adverse events.

The NCI CIRB Initiative consists of three sub-panels, all under a uniform administrative structure provided under a contract mechanism. The CIRB has three panels: one for adult late phase trials, one for pediatric trials, and one focused on adult early therapeutic trials. The adult early phase therapeutics panel will review all clinical trials conducted by the ET-CTN. All ET-CTN Sites must agree to utilize the ET-CTN sub-panel of the CIRB as the IRB of record. Participating ET-CTN institutional investigators and other staff are encouraged to participate as members of the ET-CTN CIRB sub-panel with the goal of having representation on the ET-CTN sub-panel from each participating institution. Initially, NCI CIRB review was done via a "facilitated review" process that streamlined local IRB review of adult and pediatric national, multi-center cancer treatment trials. In 2012, the NCI conducted a pilot program to change the model for the NCI CIRBs to that of a full IRB (i.e., single IRB of record) for participating institutions which was well accepted**. This independent model is now the NCI CIRB operating model and all current members of the NCI CIRB will be transitioned over to the new model in 2013.**Additional information on the NCI CIRB is available at: www.ncicirb.org.

In December 2012, the Association of the Accreditation of Human Research Protection Programs (AAHRPP) awarded the NCI CIRB with its independent model Full Accreditation. Information on the announcement of accreditation is available at: http://www.cancer.gov/newscenter/newsfromnci/2012/CIRBaccreditation and http://www.aahrpp.org/connect/whats-new/what's-new/2012/12/11/news-release-latest-accreditations-include-first-nih-entity-and-the-first-organization-in-taiwan

5. **NCI Advisory & Scientific Committees**

In addition to the key components of the ET-CTN that are described above and will be directly funded by the ET-CTN, other NCI grant and contracts supported Programs and their awardees, as well as NCI Advisory Committees will have important supporting roles in carrying out the research objectives of the ET-CTN. Thus, the ET-CTN awardees will be expected to interact as appropriate with such entities/programs as the DCTD Clinical Assay Development Network, Pharmacodynamics Assay Development and Implementation Section, Molecular Characterization Support, Division of Cancer Biology, SPOREs, NCI-Designated Cancer Center, Program Project Grants, Rare Diseases, and the NCI National Clinical Trials Network (NCTN).

The NCI Committees associated with clinical trials and translational research activities funded by the NCI are described briefly below. Information on the NCI Committees is available at: http://transformingtrials.cancer.gov/steering/overview. The NCI Coordinating Center for Clinical Trials (CCCT) is the administrative organization overseeing the activities of these Committees. General information on CCCT is available at: http://ccct.cancer.gov/about/overview.

A. NCI Clinical Trials and Translational Research Advisory Committee (CTAC):
The NCI CTAC is an external oversight committee, governed by the provisions of the Federal Advisory Committee Act, which advises the NCI Director on the NCI-supported national clinical and translational research enterprises, including both intramural and extramural research. Committee members include leading authorities in clinical trials and translational

research. The CCCT Director serves as the Executive Secretary for CTAC and the CCCT staff facilitates operations. General information on CTAC is available at: http://deainfo.nci.nih.gov/advisory/ctac/ctac.htm.

The CTAC Strategic Planning Subcommittee for the ET-CTN evaluates the clinical trial portfolio across the entire ET-CTN and provides recommendations to CTAC regarding the evaluation/prioritization decisions of the NCI Scientific Steering Committees (e.g., NCI disease-specific Steering Committees, Clinical Imaging Steering Committee) and reviews the overall trial portfolio for gaps and balance among the different disease areas and modalities.

B. NCI Investigational Drug Steering Committee (IDSC):
The NCI IDSC strives to enhance the NCI's entire clinical trials enterprise through implementation of prioritization and scientific quality initiatives under the purview of the NCICTAC.

As part of that process, the IDSC evaluates/prioritizes early phase clinical trials and pilots conducted by the ET-CTN. The IDSC is composed of leading cancer experts and advocates from the extramural community, ET-CTN representatives, and NCI senior investigators who meet regularly to:

i. Provide review and input on drug development plans.
ii. Increase the transparency and openness of the trial design and prioritization process.
iii. Enhance patient advocate and community oncologist involvement in clinical trial design and prioritization.
iv. Convene clinical trials meetings to identify critical questions, unmet needs, and prioritize key strategies.

This Committee may establish one or more Task Forces and/or Working Groups that focus on specific scientific areas of interest. General information on the NCI IDSC is available at: http://transformingtrials.cancer.gov/steering/overview.

C. NCI Clinical and Translational Research Operations Committee (CTROC):
CTROC, an internal NCI advisory committee composed of representatives from NCI Divisions, Offices, and Centers involved in NCI-supported clinical trials and translational research, provides strategic oversight for NCI clinical trials and translational research programs and infrastructures, including informatics. The Committee reviews and prioritizes clinical trials and translational research programs proposed by Divisions, Centers, and Offices to coordinate efforts Institute-wide.

1.III.1. General Management & ET-CTN Operating Principles

1.III.1.A. General Management

Direct programmatic oversight of the ET-CTN is provided by the NCI, DCTD and its programs. The Associate Chief of IDB within the CTEP, DCTD, NCI is the ET-CTN Director. The ET-CTN Director works closely with other staff within the DCTD for the ET-CTN including representatives from the Biometric Research Branch, the Cancer Diagnosis Program, the Cancer Imaging Program, and the Radiation Research Program, DCTD, including: Clinical Assay Development Network, Pharmacodynamics Assay Development and Implementation Section, Molecular Characterization Support, Division of Cancer

Biology, SPOREs, as well as other NCI Senior Scientific and Administrative staff from all the branches within CTEP, other DCTD and NCI programs and offices, and the NCI/DCTD Senior Program Specialist to oversee the ET-CTN.

NCI Division of Cancer Treatment and Diagnosis (DCTD): http://dctd.cancer.gov/
NCI/DCTD Cancer Therapy Evaluation Program (CTEP): http://ctep.cancer.gov/
NCI/DCTD Biometric Research Program (BRB): http://brb.nci.nih.gov/
NCI/DCTD Cancer Diagnosis Program (CDP): http://dctd.cancer.gov/ProgramPages/cdp/default.htm
NCI/DCTD Cancer Imaging Program (CIP): http://imaging.cancer.gov/
NCI/DCTD Radiation Research Program (RRP): http://rrp.cancer.gov/

1.III.1.B. ET-CTN Operating Principles

The purpose of the ET-CTN is to provide a standing, consolidated, and integrated infrastructure for an experimental therapeutics program with phase 1 emphasis. ET-CTN participating institutions will collaborate with each other and with NCI to achieve the objectives of the Network. The NCI will provide centralized support for program management, centralized registration, data management, centralized IRB review, auditing, and other support for approved, early phase trials originating inside and outside the Network.

1. **Access to ET-CTN Trials and Crediting for Patients Accrual to Trials**
   ET-CTN participating institutions/sites will be able to enroll patients on all adult early experimental therapeutics trials (including selected phase 2 trials) conducted by the ET-CTN, irrespective of the specific ET-CTN site which is leading the trial and providing data management and statistical analysis.
   Note: International sites (i.e., non-U.S. sites) that are participating ET-CTN institutions/ members may not be able to participate in all ET-CTN trials because of special regulatory issues specific to the country of the international member.

2. **Submission of Data and Biospecimens for ET-CTN Trials**
   All data, as well as any biospecimens collected, for an ET-CTN trial must be sent by the institutions/sites participating in the trial to the appropriately designated laboratory/biospecimen bank that is designated in the protocol, unless an exception is approved by the NCI to accommodate the needs of a specific trial.

3. **Use of the NCI CIRB**
   All U.S. institutions/sites participating in ET-CTN trials are required to use the adult CIRB whose emphasis is on early experimental therapeutic trials. See: http://www.ncicirb.org for information on the requirements for a signatory institution under the NCI CIRBs. This requirement may be waived by the ET-CTN Director through an exemption review process if the institution/site can adequately show that ET-CTN studies can be reviewed in a timely manner by its local IRB (or other Central IRB) that is equivalent to the review timelines for the NCI CIRB (i.e., about 28 days for initial review) or if the institution/site can demonstrate other exceptional circumstances that preclude it from using the NCI CIRB. This requirement does not apply to international (non-U.S.) institutions/sites participating in ET-CTN trials (including member institutions/sites in Canada), given different regulatory requirements/procedures covering human subjects protection in other countries.

4. **Trial Proposals Originating From Outside the ET-CTN**
   ET-CTN Investigators are encouraged to collaborate with investigators outside the Network in developing and conducting clinical trials. However, NCI, CTEP is unable to provide additional funding to participating sites that are outside the Network.

1.III.1.C. Grant Funding for ET-CTN

The allowable costs under the Cooperative Agreement of the ET-CTN are described under the budget section of the application process for new applications in Part 2 of these Guidelines. In general, the funds can support costs associated with personnel (e.g., operational staff, scientific and administrative committee leaders, PIs for specific trials), travel, and other operational costs related to the conduct of clinical trials. However, costs for patient recruitment, routine patient care, laboratory tests, and reference laboratory research are not allowed under the grant funding for the ET-CTN, unless approved by the ET-CTN Director and Associate Director, CTEP, for exceptional circumstances related to a specific trial. Funding for research laboratory tests may require support from other resources, including commercial and charitable funds, and/or specific administrative supplements to the Cooperative Agreements under the ET-CTN in special situations.

1.III.1.D. Funding for Data Collection/Management and Biospecimen Collection

NCI funding for LAO's participating in all ET-CTN trials to cover the costs related to data collection/management and biospecimen collection associated with enrolled patients is provided by grant funding. LAO's are responsible for establishing subcontracts with their Integrated Components and AOs.

1.IV.1. Terms and Conditions of Award for Cooperative Agreements for ET-CTN

1.IV.1.A. General Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, Public Health Service (PHS), and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

1. ET-CTN sites are expected to lead and/or participate in multidisciplinary scientific teams during the development and implementation of the ET-CTN Drug Development Plans.
2. Development of an overall research strategy for the development of clinical trials for the ET-CTN as well as all key components related to the conduct of approved clinical trials. The awardees'

programmatic responsibilities for the conduct of the clinical research supported under the Cooperative Agreements are described in the documents listed below and subsequent modifications of these documents. These documents are incorporated by reference as program-specific Terms and Conditions of Award:

A. NCI CTEP Investigator's Handbook (Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis, NCI) available at: http://ctep.cancer.gov/handbook/index.html.
B. Guidelines for Auditing of Clinical Trials for Experimental Therapeutics Clinical Trials Network (ET-CTN) at: http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ET-CTN_Audit_Guidelines.docx.

3. Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, NIH, and NCI policies and within the limits of any accepted binding NCI/NIH collaborative agreements with biotechnology and pharmaceutical partners and as governed by NCI-approved Data Sharing Plans, and NCI-approved review for use of biospecimens collected in association with ET-CTN trials.
4. Awardees are allowed to accept funds from non-governmental sources to support ET-CTN research that is not supported in part or in full by the NCI. These funds are considered "Program Income" (e.g., additional per case data management funding supplementing the NCI/DCTD per case data management funding, support for correlative science studies that use biospecimen or image collections funded by the NCI/DCTD for trials under the ET-CTN) and must be reported under the Terms and Conditions of Award for the ET-CTN unless they are associated with an exempted category under the NIH grant policy for program income, available at: http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income.
5. All key components of the ET-CTN must report these funds to the NCI on an annual basis (in the non-competitive Type 5 application – the annual progress report) and must indicate the clinical trial that the funds are being used to support (or other functional component if the funds are not provided to support specific trials). The Terms and Conditions of Award for all the Cooperative Agreements under the ET-CTN define the operational principles under which the awardees must function to ensure the independence of the research conducted regardless of whether program income is or is not available for any of the awards.

NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

An NCI Program staff member(s) acting as a Project Scientist(s) will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. Additional NCI staff members may be designated to have substantial involvement (e.g., in the role of Project Managers). The NCI Project Scientist(s)/Managers(s) will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications. If such participation is deemed essential, these individuals will seek an NCI waiver according to the NCI procedures for management of conflict of interest.

Additionally, an NCI ET-CTN Director acting as Program Official will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. Some Program Officials may also have substantial programmatic involvement (as Project Scientists/Coordinators). In that case, the individual involved will not attend peer review meetings of

renewal (competing continuation) and/or supplemental applications or will seek an NCI waiver as stated above.

The main responsibilities of substantially involved NCI staff members include, but are not limited to, the following activities:

1. Working with ET-CTN Awardees to collaboratively manage issues associated with their participating in the conduct of clinical trials across the Network;
2. Informing the PDs/PIs of scientific opportunities resulting from NCI-supported clinical research programs and facilitating collaborations between the ET-CTN and other NCI-sponsored programs;
3. Facilitating scientific involvement in oncology treatment research, including advanced imaging research and radiation oncology research, associated with ET-CTN trials;
4. Auditing of ET-CTN sites via their membership in the ET-CTN;
5. Reviewing accrual and overall performance of ET-CTN clinical trials by the site;
6. Reviewing compliance with applicable HHS, FDA, Office of Human Research Protections (OHRP), NIH, and NCI regulations for clinical research involving human research subjects;
7. Advising awardees concerning mechanisms established for quality control of therapeutic and diagnostic modalities used in ET-CTN clinical trials; and
8. Monitoring the progress and performance of the key components of the ET-CTN.

The NCI will have access to all data (including imaging data) collected and/or generated under this Cooperative Agreement and may periodically review the data. The NCI may also review all records related to awardees' performance under the award for appropriate collection, review, and distribution of biospecimens collected in association with ET-CTN trials.

In case of insufficient patient accrual per the protocol specified, inability to meet the scientific aims of the Cooperative Agreement, or noncompliance with the Terms and Conditions of Award, the NCI reserves the right to reduce award budget, withhold support, suspend, or terminate the award.

Areas of Joint Responsibility

The cooperative agreement awardee shall, with CTEP assistance, develop appropriate early phase experimental therapeutic clinical trial protocols. PIs of the ET-CTN awards, the NCI ET-CTN Director, and CTEP Senior Investigators (Project Scientists) will be members of the ET-CTN.

ET-CTN sites will be expected to participate as active team members on drug development project teams. They will meet quarterly to review studies performed under the award and more often to participate on and provide input for the IDSC, with respect to the development of drug development plans. Areas of joint responsibility include:

1. General aspects of collaboration on study development and conduct especially with respect to compliance with federal regulations for clinical trial research and participating in activities related to the collective management of the ET-CTN, as appropriate.
2. Other programmatic responsibilities to be addressed jointly, as needed, by the ET-CTN awardees and the NCI staff.

Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution

Panel composed of three members will be convened. It will have three members: a designee of the ET-CTN Group representatives chosen from the ET-CTN Leadership without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

Note that in addition to these general rules for dispute resolution, a specific appeal process will be in place for decisions regarding approval of ET-CTN study proposals and the types of studies supported by the ET-CTN**.**

1.IV.1.B. Specific Terms and Conditions of Award

General rights and responsibilities for the ET-CTN are described in RFA-CA-006. The following specific terms and conditions of award are described below. The following specific special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, Public Health Service (PHS), and NIH grant administration policies.

The dominant role and prime responsibility reside with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

1.IV.1.B.1. Awardee Rights and Responsibilities

Throughout these specific Terms and Conditions of Award, research programs for "NCI Early Experimental Therapeutics Network with Phase 1 Emphasis" funded by UM1 awards are referred to as the "ET-CTN." The ET-CTN comprises the organizational structure which is composed of the awardee institution(s), including the ET-CTN sites and ET-CTN site PIs and other key personnel, all of whom agree to collaborate on research goals of the early experimental therapeutics program.

The ET-CTN is responsible for developing its specific clinical and laboratory research projects, including definition of objectives and approaches, planning, implementation, analysis, interpretations, and conclusions of studies, and publication of results. The ET-CTN will continue to develop early phase experimental therapeutic clinical trial protocols in accord with the research interests, abilities, and goals of the early experimental therapeutics program, and submit these protocols to CTEP for review prior to their implementation.

1.1 ET-CTN Sites Key Components

1.1.1 Scientific Leadership and Site Organization

1.1.1.1 Scientific Leadership–ET-CTN

Investigators in the ET-CTN shall demonstrate scientific leadership for ET-CTN trials as well as support of and participation in other ET-CTN activities in a variety of ways through their membership in the ET-CTN, including but not limited to the following:

1. Having primary responsibility for development of an overall research strategy for the development of ET-CTN clinical trials, as well as all key components related to the conduct of approved clinical trials.

2. Conducting high-quality trials evaluating novel treatments with innovative translational components.
3. Offering eligible patients participation in ET-CTN studies and entering sufficient patients to meet accrual targets and enrollment of patients on ET-CTN trials.
4. Participating in research design and protocol development for ET-CTN studies, including nomination of IDSC Project Team members and engaging in collaborations between other ET-CTN sites and NCI-supported programs and investigators, particularly at their institution, that may lead to an ET-CTN trial.
5. Analyzing and disseminating trial results, including PK/PD and molecular characterization.
6. Acquiring high-quality biospecimen(s) for analysis of integral and integrated biomarkers.
7. Participating in major meetings of the ET-CTN, including NCI Early Drug Development Meetings and other meetings deemed necessary for performance of the activities of ET-CTN.
8. LAO PI(s) are responsible for accrual to all trials conducted across the ET-CTN.
9. Collaborating with NCI in managing the ET-CTN, including but not limited to, participating in the CIRB, utilization of NCI support services, Medidata Rave, monitoring, and auditing.
10. The LAO is responsible for coordinating all the scientific and administrative policies at the institution.
11. LAO PI(s) of all ET-CTN awards shall serve on the NCI-sponsored panel, IDSC task forces and committees. The IDSC conducts strategic discussions regarding early phase experimental therapeutics drug development trials involving agents for whom CTEP holds an IND. IDSC participants will commit up to 12 days per year to IDSC activities. This commitment includes attendance at quarterly in-person meetings and teleconferences, and participation on task forces and committees.
12. The awardee and up to two additional individuals are required to attend the Early Therapeutics Development Meetings sponsored by CTEP. The awarded ET-CTN site PIs are required to attend the bi-annual IDSC meetings.
13. Timely publication of major findings is central to the ET-CTN mission and is a primary means by which the ET-CTN's accomplishments can be evaluated. The ET-CTN will have timelines for the development of abstracts and manuscripts based on its clinical trials and should have mechanisms for monitoring the performance of the ET-CTN in meeting these timelines. Corrective action plans will be implemented when these timelines are not met. Publication or oral presentation of work conducted via the ET-CTN requires appropriate acknowledgment of NCI support. For publications using an agent supplied under a Cooperative Research and Development Agreement (CRADA) or Clinical Trial Agreement (CTA), the CTEP pharmaceutical collaborator will have an opportunity for review prior to submission, as per CTEP Standard Protocol Language for CRADAs and CTAs. The NCI will have access to all data generated under this cooperative agreement and will periodically review the data.

1.1.1.2 Scientific Leadership – ET-CTN sites

Investigators in the ET-CTN sites shall demonstrate scientific leadership for ET-CTN trials as well as support of and participation in other ET-CTN activities in a variety of ways through their membership in the ET-CTN, including but not limited to, the following:

1. It is anticipated that the ET-CTN Site PI(s) will possess expertise in experimental therapeutics and be well integrated into the scientific and administrative senior leadership in clinical research, thereby fostering collaboration between the ET-CTN and other clinical and translational research investigators. ET-CTN Site PI(s) should be well integrated into the scientific and clinical activities of other NCI clinical trials mechanisms.

2. Leading and participating in the IDSC Project Teams for drug development of individual experimental therapeutics.
3. All participating ET-CTN sites shall be responsible for screening, enrolling patients, collecting required biospecimens, treating patients, and monitoring and reporting safety information throughout the conduct of their clinical trials.ET-CTN sites will be able to enroll patients on all ET-CTN trials open within the ET-CTN irrespective of the specific Institution (LPO) which is leading. **Note:** International sites (i.e., non-U.S. sites with the exception of Canada) that are AOs may not be able to participate in all ET-CTN trials because of special regulatory issues specific to the country of the international member or based on the decision of the pharmaceutical collaborator.
4. Establishing fiscal management arrangements to support ET-CTN-related activities at each Integrated Component and AO (if applicable).
5. Establishing fiscal management of the administration of the PK/PD component, including the process for selecting laboratories to perform specific studies (a competitive process is encouraged when feasible).
6. The LAO is responsible for the financial management of the ET-CTN sites, including appropriate funding for all activities and provision of appropriate NCI/DCTD approved total cost for various categories of funding to member institutions/sites through purchase service agreements or subcontracts as well as funding for other important scientific and administrative services needed for ET-CTN functions such as support for the LPO.
7. The LAO should ensure that the funding is allocated at the site so that investigators and clinical research staff from different departments and disciplines at the institution that participate in ET-CTN trials are appropriately represented in the disbursement of funding. For example, the PI(s) at an institution/member site, with which an LAO has a subcontract or purchase service agreement (PSA) for work related to enrollment of patients and conduct of trials in the ET-CTN, may be a member of the Medical Oncology department at the institution, yet work under the subcontract or PSA is performed across multiple departments at the institution (e.g., surgery, pathology, radiation oncology). The LAO should strive to ensure that all member institutions/sites distribute funding to all departments involved in support of ET-CTN clinical trials in a manner that reflects the work performed by the various members of the clinical research team.
8. Any separate, non-NCI/DCTD funding (i.e., funding not provided under the Cooperative Agreements of the ET-CTN) dispensed by a LAO to cover costs associated with patient enrollment on ET-CTN trials must be provided to all qualified institutions/sites that participate in its ET-CTN trials regardless of which LAO the enrolling institution belongs to and/or credits with the patient accrual. This principle is considered an essential feature of the ET-CTN and the Terms and Conditions of Award as it is fundamental to ensure fairness for work performed across the ET-CTN.
9. Establishing a process for the distribution of funds from the Coordination of Clinical Trials and Associated Activities component to AOs to support special clinical research costs for patients accrued onto ET-CTN clinical trials.
10. Accomplish collaboration between all participating ET-CTN sites and other clinical and translational research investigators locally, nationally, and internationally.ET-CTN Sites shall provide a mentorship program or activities to involve young investigators at their institution in clinical trial research and to help train them to eventually take on senior leadership responsibilities for components of clinical trial research at the institution.
11. Establishing procedures to allow non-ET-CTN institutions to participate in the development and conduct of early phase experimental therapeutic trials in those limited situations in which an

institution has distinctive expertise or capabilities that would contribute to successful conduct of a program study.

1.1.1.3 Site Organization

Under the direction and leadership of the PI(s), the LAO is responsible for development and maintenance of a governance and organizational structure to coordinate ET-CTN site activities at the institution. The organizational structure of the ET-CTN sites should have the following attributes:

1. Be established with clear and appropriate staff roles and reporting responsibilities, especially with respect to the role and reporting responsibilities of any multiple PIs.
2. Establish and maintain site, investigator, and associate rosters with the CTSU.
3. ET-CTN site PI(s) should be well integrated into the scientific and clinical activities of each of the NCI clinical trials mechanisms such as Cancer Centers and SPORE(s).
4. The AO is under the leadership of the Site PI(s), who coordinate(s) all the scientific and administrative policies at the institution related to ET-CTN activities, as well as coordination with the Coordination of Clinical Trials and Associated Activities Component and other ET-CTN sites.

1.1.2 Team Science for Project Development

ET-CTN Sites are expected to lead and/or participate in multidisciplinary scientific teams during the development and implementation of ET-CTN drug development plans.

1. The PI of the LAO (in his/her role as an IDSC member) will be expected to serve as the leader of IDSC Team(s) charged with the design, implementation, and conduct of drug development plans.
2. Each IDSC Team will focus on the development of a specific experimental therapeutic to understand its molecular mechanisms, and will consist of the NCI Senior Scientist and experts in a broad range of scientific areas, such as cancer biology, translational science, oncology, statistics, assay development, and molecular characterization.
3. IDSC Team drug development plans may include multiple distinct clinical trials, each headed by a LPO PI.
4. IDSC Team leaders will be expected to provide strong leadership and management of these diverse collaborative teams for the duration of the development of the experimental therapeutic.

1.1.3 PK/PD, Biomarker Assays, and Molecular Characterization of Patients

ET-CTN sites will comply with all ET-CTN requirements for the PK/PD and molecular analyses during the conduct of ET-CTN trials.

When scientifically appropriate, ET-CTN sites may act as a central resource for the PK/PD, or molecular analyses specific to an ET-CTN clinical trial. In those cases, the ET-CTN site will:

1. Work with the NCI to provide the scientific and logistical infrastructure to receive, store, and analyze clinical samples from all ET-CTN sites participating in that trial.
2. Be responsible for timely and accurate transmission of data generated from those analyses to the NCI.

The NCI will have access to all data (including molecular characterization and genomic/proteomic data, PK/PD, and imaging data) collected and/or generated under this Cooperative Agreement and will periodically review the data.

1.1.4. Coordination of Clinical Trials and Associated Activities

ET-CTN Sites are expected to have experience and expertise in the management of complex early phase clinical trials, including protocol development, patient screening and enrollment, data and specimen

collection and management, and compliance with regulatory requirements related to human subject protections and privacy and FDA-regulated investigational agents.

A. Protocol Development

1. The LPO shall submit an LOI for review and approval prior to protocol development. Protocols for review and approval by NCI shall be preceded by a written LOI to the CTEP LOI Coordinator declaring interest in conducting a particular study. LOIs shall be submitted using the LOI template (LOI Submission Form).
2. The LAO SOPs should include timelines for the steps involved in the writing and electronic submission of LOIs as part of the IDSC project team and clinical protocols, and should include mechanisms for monitoring the performance of the LPO in meeting these timelines. The LAO's SOPs should include corrective action plans outlining the steps to be taken when these timelines are not met. Data concerning the early phase experimental therapeutic program's performance in meeting timelines for protocol development should be provided in the Annual Progress Report and quarterly tabular updates.
3. It is the responsibility of the LPO to develop the details of the research design of the protocol, including definition of objectives and approaches, planning, implementation, analysis, interpretations, and conclusions of studies, and publication of results.
4. Clinical trial protocols should be developed, submitted, and implemented in accordance with the DCTD "Investigator's Handbook" (http://ctep.cancer.gov/handbook/). Reference protocol development guidelines (See: http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf).
5. The LAO shall not expend NCI funds to conduct any study disapproved by CTEP unless CTEP's disapproval has been modified by the arbitration process (see Section IV, page 49, Arbitration Process).
6. The LAO is responsible, in accordance with the program's SOPs, for the preparation and implementation of procedures for development and submission of early phase clinical trial protocols to the CTEP Protocol and Information Office (PIO) in a timely fashion for NCI's review and approval.
7. The LAO is responsible for establishing routine electronic communication with ET-CTN sites to facilitate clinical trial protocol development, study monitoring, and work of the Coordination of Clinical Trials and Associated Activities component. Relevant communication methods include website postings, e-mail, teleconferences, and video conferences.
8. The LAO is responsible for communicating the results of the CTEP Protocol Review Committee (PRC) to relevant ET-CTN site members and the LPO PI.
9. All clinical trials utilizing CTEP-sponsored investigational agents co-developed with a pharmaceutical collaborator shall be conducted in accordance with the terms of the "Intellectual Property Option Policy" (April 1, 2011) and the NCI Standard Protocol Language for Cooperative Research and Development Agreements (CRADAs) and Clinical Trial Agreements (CTAs). Foreign site participation is dependent on approval of the pharmaceutical collaborator and the foreign site's successful regulatory filing with the foreign health authority.
10. Individuals may be asked to participate on the NCI CIRB. Participants may be, but are not limited to, physicians, nurses, patient advocates, and ethicists.

B. Correlatives

The LAO is responsible for managing and coordinating the acquisition and shipping of protocol-specified tumor specimens and biological fluids (with relevant de-identified clinical data as indicated) to the appropriate laboratories and/or tumor/specimen repository or at the ET-CTN site for storage of

specimens for future research laboratory studies. The LAO is responsible for validation of all assays in the appropriate laboratory environment, and reporting PK/PD, biomarker assays, and molecular characterization assay study results.

1. All biospecimens collected for an ET-CTN trial must be sent by the institutions/sites participating in the trial to the designated ET-CTN laboratory unless an exception is approved by the NCI/DCTD to accommodate the needs of a specific trial.
2. The LAO is responsible for overseeing the timely collection and transmission of biospecimens from all its Integrated Components and AOs to ET-CTN trials for patients that are credited to the ET-CTN Site.
3. Timely reporting of data to CTEP shall be done using CTMS or Clinical Data System (CDS) https://cdsweb.nci.nih.gov/cdsweb/loginPage.do. All ET-CTN studies using CTEP IND agents will report bi-weekly using CTMS Medidata Rave.
4. Biospecimen Sharing Policy: The LAO is required to follow the NCI/DCTD policy regarding review of requests for use of banked biospecimens collected in association with ET-CTN trials by CTEP's PRC or an NCI/DCTD-approved ET-CTN Correlative Science Committee. The LAO is required to have a plan/policy in place to describe how information on its inventory of biospecimens will be made available to the public that is submitted to and approved by the NCI ET-CTN Director, Associate Director CDP, and Program Director of the Tumor Banking Program for the ET-CTN. This inventory should be consistent with standards established by the NCI ET-CTN Biomarker Review Committee (BRC).

C. Data Management

The LAO, under the direction of the LAO PI, is responsible for coordinating clinical protocol development, protocol submission for review and approval, study conduct (including central data collection and analysis by services and tools provided (e.g., Medidata Rave, OPEN, RSS, CTMS), QA including QC and study monitoring, protocol amendments/status changes, adherence to requirements regarding investigational drug management and federally mandated regulations, and protocol and performance reporting. Specific responsibilities are:

1. Study Monitoring:
   http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm.
   The LAO or LPO in collaboration with CTMS is responsible for assuring accurate and timely monitoring of the progress of each study and, therefore, must adhere to the standard procedures for timely data collection and data management consistent with the intensive data requirements and the need for rapid reporting necessary for early phase studies. Standard procedures include (but are not limited to):
   a. Precise tracking of patient accrual and adherence to accrual goals defined by the clinical trial protocol. If the ET-CTN wishes to continue accrual to a study beyond the total accrual goal for eligible and ineligible patients specified in the clinical trial protocol, the LAO shall seek approval from CTEP prior to continuing patient accrual. Accrual will be an important measure of success and will be considered in the context of using novel trial designs, such as accelerated titration designs that accrue fewer patients than 3 X 6 cohort expansion studies, timely accrual, and completion of study objectives outlined in the protocol.
   b. Procedures for assigning dose level (for dose escalation studies) at the time a new patient is enrolled in a study, and assuring that the required observation period has elapsed before beginning a higher dose level.
   c. Patient screening and assessment of patient eligibility and evaluability.

d. Adequate measures to ensure timely medical review and assessment of individual patient data.
e. Adequate measures in place to ensure timely submission of clinical trials data (e.g., adverse events, anticancer response, etc.) and responses to data queries from all participating ET-CTN sites due to the stringent safety requirements for early experimental therapeutic trials. These measures should include procedures for monitoring compliance with the ET-CTN's guidelines for data timeliness on an institution and a study basis, including summary reports of data submission timeliness to be used for Institutional Performance Review and to be used for study monitoring. These summary reports shall be included in the Annual Progress Report.
Failure to comply with timely submissions and query resolution may result in temporary suspension of site accrual and require submission of Corrective Action and Preventive Action (CAPA) plan.
f. Timely reporting of treatment-related morbidity/mortality information and measures to ensure communication of this information to all relevant parties. For investigational agents sponsored by CTEP, this involves reporting to IDB via CTEP AdEERS according to CTEP guidelines specified in each protocol (http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers).
g. Preparation of study monitoring reports describing patient accrual and demographics, data timeliness, toxicity, and other items as appropriate using reports accessible through the Reporting Module in CTMS. Examples of study monitoring reports include reports prepared for study chairs, the annual reports for program meeting agendas, and reports for the Data and Safety Monitoring Committee (DSMC) (if one has been constituted).
h. Adequate policies and procedures for closure of studies. If the ET-CTN wishes to close accrual to a study prior to meeting the initially established accrual goal, the interim results and other documentation should be made available to CTEP staff for review and concurrence prior to implementation of the decision. It is recommended that statistical guidelines for early closure be presented as explicitly as possible in the clinical trial protocol in order to facilitate these decisions.
i. Within 45 days of study completion (all patients have completed protocol-defined therapy), molecular, imaging or correlative study analyses have been completed and the 30-day safety reporting interval (unless defined differently in the protocol) has been met. Within 45 days of study completion, all data and query resolutions from ET-CTN sites shall be entered in Medidata Rave.

2. Data Management Policies and Practices: The responsibilities of the Coordination of Clinical Trials and Associated Activities component for data management related to study monitoring include the following:
   a. Providing for central storage, security, processing, and retrieval of study results.
   b. Incorporating security features consistent with the guidelines of the U.S. Department of DHHS http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/hitechnprm.html.
   c. Implementing procedures for backing up the ET-CTN clinical and administrative data, including intermittent duplication of the database with storage at a remote facility.
   d. Protecting patient confidentiality at all steps in the submission and analysis of clinical trials data and ensuring the technical integrity and security of the data management systems.

e. Providing CTEP in a timely manner, upon the request of the Program Director, true copies of data files and supporting documentation for all CTEP-supported protocols that have a major impact on patterns of care, as determined by CTEP.
f. Providing verification of pathological diagnosis in cases where known variability in the accuracy of histological diagnosis is a potentially serious problem and where pathology data may provide important prognostic information.
g. Providing review either concurrently or retrospectively of port films and compliance with protocol-specified doses for individual patients, where relevant. Determination of the adequacy of radiation delivery with the assistance of their respective radiological physics center, whose functions usually include equipment dosimetry, periodic institutional visits, and other aspects of physics review.
h. Providing review of pharmacy orders, drug administration, flow sheets, and drug distribution with determination of protocol compliance in dose administration and dose modification.
i. Providing assessment of adequacy of protocol-specified surgical procedures through review of operative notes and study-specific surgical forms where relevant.
j. Providing assessment of adequacy of protocol-specified imaging procedures. This assessment may include methods for acquisition and display of images, methods for monitoring quality of image interpretation (including quantitative measurement of lesions), and methods of data archiving and retrieval as appropriate to specific studies.
k. Establishing assay validation and QA/QC procedures for laboratory assays for PK/PD and other molecular assays. These procedures may include such elements as assay validation procedures, calibration curves, check samples, standards for accepting or rejecting data (e.g., positive and negative controls), and external QA/QC. Procedures for ensuring patient privacy and sample tracking must be established.
l. Reporting of PK/PD, biomarker assays, and molecular characterization assay results in real time during the course of the study. The schedule for sample assay should be established in the written protocol.

D. Regulatory

The LAO is responsible for ensuring that it and the ET-CTN sites are in compliance with all applicable federal regulations concerning the conduct of research involving human subjects. LAOs shall have policies and procedures for ensuring compliance with federal regulations for the protection of human subjects. These include the following policies and guidelines to be addressed:

1. Human Subjects Research
   A. OHRP Assurances: The LAO must assure that it and each Integrated Component and AO has a current, approved Federal wide Assurance (FWA) on file with OHRP. The LAO is responsible for assuring that it and the ET-CTN Sites are in compliance with all applicable federal regulations concerning the conduct of human subjects research. Policies and guidelines to be addressed include the following:
      i. The LAO must assure that each member (this includes all ET-CTN sites enrolling patients in ET-CTN trials) has a current, approved FWA, on file with OHRP http://www.hhs.gov/ohrp/assurances/status/index.html. Information on assurances is available on the OHRP website at: http://www.hhs.gov/ohrp/. Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to risks to the subjects, the adequacy of protection against

these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

ii. Assuring Appropriate Informed Consent: The LAO must assure that each patient (or legal representative) gives written informed consent prior to entry on study. Ensure any substantive modification by the AO of sample consent information related to risks or alternative procedures is appropriately justified.

iii. The ET-CTN sites must have procedures in place to ensure that each site is trained and understands the policies and procedures relevant to ensuring that patients are enrolled on studies with appropriate informed consent per NCI/NIH policy and federal regulations. The template for the NCI informed consent document must be used for all ET-CTN trials, with appropriate modifications as approved by NCI/DCTD for specific trials during the protocol development and review process. Information on the NCI informed consent templates is available on the CTEP website on the "Protocol Development" page in the Informed Consent section.:

iv. Management, data analysis, and data and safety monitoring (DSM) systems are adequate, given the nature of the research involved.

v. Sample protocols and informed consent documents are developed and distributed to each Integrated Component and AO.

vi. The Investigator's Handbook, a Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis (DCTD) (and any subsequent modification to it) is hereby incorporated by reference as terms of award. This document describes the programmatic responsibilities for the conduct of the research supported by this cooperative agreement. http://ctep.cancer.gov/handbook/

vii. Education on the Protection of Human Subjects: NIH policy requires education on the protection of human subjects for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. This policy is available on the NIH website at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

2. Institutional Review Board

A. CIRB Review of ET-CTN Protocols: The LAO must assure that each clinical trial protocol is reviewed and approved by the NCI CIRB prior to patient entry, and must ensure that each clinical trial protocol undergoes continuing review no less than once per year as long as the clinical trial is active.

B. Exemption requests with supporting documentation of the timely IRB review from member institution/sites of the ET-CTN must be submitted to the NCI ET-CTN Director by the supporting LAO. If an exemption is granted, the Coordination of Clinical Trials and Associated Activities component is responsible for including reports of IRB timelines for their sites that have received an approved exemption in its annual progress report as well as any other pertinent information. The NCI ET-CTN Director may withdraw the exemption and require that the institution/site use the NCI CIRB for applicable ET-CTN studies if justification for the exemption is not warranted on a continuing basis.

C. The LAO must ensure that each ET-CTN site forwards its regulatory documents to the CTSU RSS; otherwise, the site shall not be allowed to enroll patients on ET-CTN trials. If an ET-CTN site receives a waiver for NCI CIRB review, the LAO must assure that each protocol for an ET-CTN trial that one of its sites credits to the LAO is reviewed and approved by the NCI CIRB, or, if appropriate, the local IRB of the ET-CTN prior to patient entry via the CTSU RSS, and

assure that each protocol is reviewed annually by the ET-CTN site IRB so long as the protocol is active. (It is anticipated that the NCI CIRB will be the IRB of record in most cases.)

D. IRB review of the LAO cooperative agreement application is required upon award. The IRB should determine and document that the Coordination of Clinical Trials and Associated Activities component has sufficient mechanisms in place to ensure that:
   i. oversight of data management and analysis are adequate, given the nature of the research involved;
   ii. sample protocols and informed consent documents are developed and distributed to each institution/site participating in a trial;
   iii. each institution/site holds or is covered under an applicable OHRP-approved Federal-Wide Assurance (FWA);
   iv. each protocol is reviewed and approved by the CIRB (or IRB with approved waiver) covering the member institution/site prior to the enrollment of subjects;
   v. any substantive modification by the institution/site of sample consent information related to risks or alternative procedures is appropriately justified; and
   vi. informed consent is obtained from each subject in compliance with DHHS regulations. Information on this requirement for IRB review can be obtained on the OHRP website at: http://www.hhs.gov/ohrp/.

3. Registrations
   A. All ET-CTN site investigators performing trials involving CTEP investigational agents must be active NCI-registered investigators and have completed and submitted all required investigator registration documents (Form 1572, Financial Disclosure Form, Supplemental Investigator Data Form, and Curriculum Vitae). See "Investigator Registration" at: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm
   All orders for CTEP IND agents must be signed or co-signed by an NCI-registered investigator.
   B. Clinical Trials Reporting Program (CTRP)/clinicaltrials.gov Registration and Outcomes Reporting: All ET-CTN trials must also be registered and appropriate information updated in the NCI CTRP as described at: http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main as well as registered in the U.S. National Library of Medicine clinical trials database (i.e., at: www.clinicaltrials.gov). Changes in the trial design and accrual, as well as results reporting from ET-CTN trials are to be reported to clinicaltrials.gov as required under the Food and Drug Administration Amendments Act (FDAAA), Section 801. LPO should work with its associated ET-CTN sites to coordinate activities to ensure information on ET-CTN trials is appropriately updated.

4. Safety Reporting
   A. Assuring timely reporting of all serious and/or unexpected adverse events. For investigational agents sponsored by CTEP, this involves reporting to IDB, CTEP, via AdEERS according to CTEP guidelines specified in each clinical trial protocol http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers. The regulation for expedited adverse event reporting is 21CFR 312.32.
   B. Adverse Event Reporting and Patient Safety: The ET-CTN sites must utilize AdEERS, or its successor application, for reporting of all serious adverse events to ensure potential patient safety issues can be identified and addressed quickly. Adverse events should be reported using the CTCAEv4.0 or most recent version, which is NCI and DCTD's standard language for reporting adverse events in oncology clinical trials.

C. Serious adverse event reporting for all ET-CTN trials should follow the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

D. For studies with immediate safety issues that are under monitoring by a Data and Safety Monitoring Plan or Data Monitoring Committee (DMC):
   i. Immediate notification should be made to the DMC Chair and the NCI ET-CTN Director as described in the approved Data and Safety Monitoring Plan.
   ii. For therapeutic studies that are not under DMC monitoring, immediate notification should be made to the Senior Investigator in the IDB at CTEP (along with the agent liaison physician in the IDB at CTEP for studies being conducted under a CTEP IND) with a copy to the NCI ET-CTN Director.
   iii. For imaging studies that are not under DMC monitoring and/or those being conducted under a CIP IND, immediate notification should be made to the imaging agent liaison physician in the Clinical Trials Branch at CIP with a copy to the NCI ET-CTN Director.
   iv. The Coordination of Clinical Trials and Associated Activities component is required to send a listing (or an email with internet access link to a listing) of all DMC recommendations accepted by the NCI ET-CTN Director after every scheduled DMC meeting. DMC recommendations accepted by the LAO PI(s) after ad hoc DMC meetings/calls must be communicated to the NCI ET-CTN Director.
   v. The LAO must establish a Data and Safety Monitoring Plan (DSMP)for the clinical trials conducted by the ET-CTN Sites in compliance with NIH and NCI guidelines for data and safety monitoring for clinical trials (see: http://grants.nih.gov/grants/guide/notice-files/not98-084.html, with additional description at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html and the NCI policy at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines). Any changes/modifications to the plan must be submitted to and approved by NCIET-CTN Director.

E. For early experimental therapeutic studies using CTEP IND agents, CDUS Complete reporting procedures will be used, which capture demographic, adverse event information (by course), and response data. See: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm.

5. Policy Compliance

A. For any study using agents under a CTEP or other DCTD-sponsored IND, any increase in the incidence of expected toxicities and any plans to change a trial design or close a trial early due to toxicity should immediately be discussed with the IDB at CTEP or the Clinical Trials Branch at CIP if a CIP IND imaging agent is involved before any action is taken.

B. NIH policy requires that women and members of minority and ethnic subgroups be included in all NIH-supported biomedical and behavioral clinical research projects involving human subjects, as described at: http://grants.nih.gov/grants/funding/women_min/women_min.htm. Compliance with this policy requires appropriate study designs, targets for total protocol accrual with distribution by ethnic/racial categories and by sex/gender, as well as reporting of accrual by ethnic/racial categories and by sex/gender. Since ET-CTN sites conduct multiple clinical trials, the amended NIH Policy on inclusion of women and minorities in research also applies (see NIH Guide Notice on NIH Guidelines on the Inclusion of Women and Minorities as Subjects in

Clinical Research – Amended October 2001 at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html, with a complete copy of the updated Guidelines available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

C. A description of plans to conduct analyses, as appropriate, by sex/gender and/or ethnic/racial categories must be included in clinical trial protocols. Cumulative subject accrual and progress in conducting subset analyses must be reported to NIH in the annual progress reports. The LAO shall report this data for all patients enrolled on studies it leads regardless of whether it is credited with the patient enrollment or not and this data should be reported in the annual progress reports.

D. NIH policy requires that children (i.e., individuals under 21 years of age) must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. For cancer clinical research, ET-CTN Sites conducting research in adult cancers can provide a rationale for not including children because the majority of children with cancer in the United States are already accessed by Network Sites devoted to pediatric cancer research. Requiring inclusion of children in the proposed adult study would be both difficult and unnecessary (since the research question is already being addressed in children by the pediatric network) as well as potentially counterproductive since fewer children would be available for the pediatric network study if other studies were required to recruit and include children.

E. Applicants must abide by the Code of Conduct as provided (To Be Provided).

F. Conflict of Interest Policy: The LAO must establish a Conflict of Interest Policy that is in compliance with all of the DHHS regulatory requirements for conflict of interest as outlined by NIH grants policy available at: http://grants.nih.gov/grants/policy/coi. This policy should ensure that there is no reasonable expectation that any investigator or staff member of the ET-CTN sites involved in the design, conduct, or reporting of research will be biased by any conflict of interest (using the definition of investigator provided in the NIH grants policy). This policy should be in compliance with NCI/DCTD/CTEP's Conflict of Interest Policy for ET-CTN Clinical Trials found on the CTEP website at: http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies.

G. Other Federal Regulations: Information on other federal regulations (and their associated citations/URLs) that may be applicable to ET-CTN research is provided in Part 4: Appendices.

h. The NIH Public Access Policy ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central *upon acceptance for publication*. To help advance science and improve human health, the Policy requires that these papers are accessible to the public on PubMed Central no later than 12 months after publication. More information about this policy or the submission process is available on the NIH Public Access Policy website at: http://publicaccess.nih.gov/.

6. Data-sharing

A. The *Intellectual Property Option to Collaborator* document (and any subsequent modification to it) is hereby incorporated by reference as terms of award. This document describes the programmatic responsibilities for the conduct of the research supported by this cooperative agreement and can be found at: http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations or may be obtained from the Regulatory Affairs Branch, CTEP, DCTD, NCI, at telephone number (301) 496-7912.

B. Clinical trials data must be directly submitted by performing institutions using the CTMS electronic data capture systems (ACESR or CDS, AdEERS, or CaAERs).
C. Monitoring activities must be conducted to guarantee data integrity and compliance with protocol and regulatory requirements.
D. Since it is expected that all data on patients enrolled on ET-CTN site trials will be transmitted to the appropriate LAO, those LAOs should address data sharing plans that will be applied to the patient data from the ET-CTN Sites. All LAO data-sharing plans should comply with the NIH Data-sharing Policy as described in http://grants.nih.gov/grants/policy/data_sharing.
E. Data-sharing Policy: The LAO should address a plan for sharing research data; http://grants.nih.gov/grants/policy/data_sharing. The LAO's policy for data sharing will be subject of approved by the NCI ET-CTN Director. Per this policy, requests for data will only be considered once the primary study analyses have been published.
F. Requests for data from clinical trials, conducted under a binding collaborative agreement between NCI/DCTD and a pharmaceutical/biotechnology company, that are not under DSMB monitoring but are not yet subject to the Data-sharing Policy (e.g., because the primary study analyses have not yet been published) must be in compliance with the terms of the binding collaborative agreement and must be approved by NCI/DCTD (i.e., the NCI ET-CTN Director in conjunction with the NCI/DCTD Regulatory Affairs Branch). Release of data may be subject to the terms of any contracts the LAO has with other entities which cover any of the requested data.
G. Institutional Support (Facilities, Equipment, and Programs): The ET-CTN Site facilities, equipment, and programs should include comprehensive medical training programs and preclinical laboratories that perform basic research to help foster collaborations with the clinical investigators at the site who participate in the ET-CTN that will enhance ET-CTN research.

1.1.5 Research Pharmacy Management

ET-CTN Sites must have established procedures for investigational pharmacy operations to adequately fulfill obligations related to investigational agents. These obligations and requirements include, but are not limited to, the following elements.

1. Policies/Procedures
   A. Access to approved protocol documents and amendments and notification of protocol activation at the site.
   B. Notification of patient enrollment to a given protocol, including notification of signed informed consent prior to agent dispensing.
   C. Order and receive agent(s) from the supplier as instructed in the clinical protocol.
   D. Agents are available when needed.
   E. Policies and procedures for safe and secure handling, preparation and disposal of dangerous goods, hazardous substances, and infectious substances.
   F. Policies and procedures related to safe transport of investigational agents within the facility or to approved satellite facilities.
   G. Proper documentation of agent transfer to another NCI-sponsored trial and/or final disposition of investigational agents.
   H. Adherence to local, state, and federal regulations and laws.
   I. Continuous training of staff and written training documentation.
   J. Written SOPs related to investigational agent management, including agent receipt, accountability, and final disposition. Written procedures regarding authorized dispensing of investigational agents to eligible study subjects on approved protocols.

K. Procedures to ensure NCI-supplied investigational agents are only prescribed by physicians who are registered and have an active registration status on file with the Pharmaceutical Management Branch, CTEP.
L. Procedures for reconciling deviations.
M. The ability to properly order, receive, store, and maintain investigational agents.
N. Safe and secure handling, preparation, and disposal of dangerous goods, as well as hazardous and infectious substances.
O. Written SOPs related to investigational agent management.
P. Existing procedures for reconciling deviations.
Q. Procedures for assuring that the ET-CTN sites are in compliance with CTEP requirements described in the DCTD Investigators' Handbook for storage and accounting for investigational agents [including NCI/HHS Drug Accountability Records (DAR) procedures] and are in compliance with FDA requirements for investigational agents.

2. Infrastructure/Equipment
   A. Availability of secured access storage space and storage unit(s) necessary to meet storage conditions of agent(s), including controlled room temperature, refrigerator (2 to 8°C), freezer (-10°C to -20°C), and ultralow freezer (-70°C) storage.
   B. Maintenance of continuous proper storage conditions of agent(s) according to supplier instructions, including validation documentation such as temperature logs or temperature recordings and access to emergency back-up power supplies.
   C. Ability to store and segregate agents by protocol, strength, unit, formulation, and investigator.
   D. Adequate security of agent(s) with controlled access to authorized personnel.
   E. Accurate completion of NCI's DARF, NIH-2564, http://ctep.cancer.gov/forms/ as the primary record of all transactions related to the investigational agent(s).
   F. Limited access areas for secure and safe preparation of investigational agents.
   G. Access to appropriate primary containment equipment, personal protective equipment, and safety equipment.
   H. Secured access to storage space and storage units(s) necessary to meet storage conditions of agent(s).
   I. Research pharmacy personnel experienced in the preparation, storage, and dispensing of investigational agents.

1.1.6 Career Development and Mentored Training of Junior Investigators

The ET-CTN Sites are responsible for having a mentorship program to involve junior investigators in ET-CTN clinical research and to help train them to eventually take on leadership responsibilities for clinical trials and/or committees. ET-CTN sites will:

1. Provide opportunities to enhance skill in and teach principles of experimental therapeutics.
2. Integrate translational science (bench-to-bedside and bedside-to-bench) into the program.

1.1.7 Performance

The LAO is responsible for submitting annual progress reports to the NCI that describe activities and accomplishments during the previous year of the ET-CTN sites. The report will use the PHS 2590 and include:

1. A summary of the overall performance of the LAO's Coordination of Clinical Trials and Associated Activities component in meeting their responsibilities for clinical trial protocol development, study monitoring, and complying with Federal regulations.

2. Summary data on performance of each Integrated Component and AO, including clinical trial accrual, quality and timeliness of submitted data, and involvement in clinical trial protocol development activities.
3. Research plans, changes in procedures and/or staff, and the proposed budget for the coming year.
4. Use of tables in the Resources section of this FOA is strongly recommended for the purpose of reporting annual progress.
5. Retain custody of and have primary rights to the raw data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, NIH, and NCI policies and within the limits of any accepted binding NCI/NIH CRADAs with biotechnology and pharmaceutical partners and as governed by NCI-approved Data-sharing Plans and NCI-approved review for use of biospecimens collected in association with ET-CTN trials.
6. Pharmaceutical and biotechnology companies will have access to all data generated under CTEP Collaborative Agreements; however, the companies may contract directly with the CTEP support contractors (CTIS and Theradex) with prior approval from NCI for access to data files or other reports not routinely provided.

1.IV.1.B.2. NIH Responsibilities

The NCI Project Scientist(s)/CTEP Program Director and additional relevant NCI staff, as needed, will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards. The NCI ET-CTN Director will be the main NCI contact for all facets of the scientific interaction with the awardees and will provide advice to the awardee on specific scientific and/or analytic issues. NCI scientific or program staff will assist, guide, coordinate, or participate in project activities.

The role of the NCI/DCTD staff, as described throughout these Terms and Conditions of Award, is to assist, facilitate, and ensure optimal coordination of ET-CTN activities. The ET-CTN is part of a larger NCI-sponsored clinical trials program that also includes investigational agent development. The CTEP staff has very specific and well-defined responsibilities for the oversight and review of ET-CTN Site clinical trials and for investigational agent development that meets DCTD/CTEP responsibilities as sponsor of INDs and IDEs as defined in the Code of Federal Regulations (CFR) 21 Part 312 and Part 812. The responsibilities of NCI/DCTD staff are described below.

NCI Program Staff Responsibilities will include:

1.1.1 Scientific Leadership

1. **The NCI responsibilities are** related to research efforts of the ET-CTN and include, but are not limited to, the following activities:
   A. Drug sponsor for investigational agent or device development for NCI-sponsored or co-sponsored IND and/or IDE clinical trials.
   B. Act as scientific liaisons to awardees in the ET-CTN and participate in drug development meetings.
   C. Informing ET-CTN investigators of scientific opportunities resulting from NCI-supported clinical research programs.
   D. Oversight of data and safety monitoring plans and boards for ET-CTN clinical trials.
   E. Oversight of data management and monitoring programs for ET-CTN trials, as well as onsite auditing programs and QA/QC programs for the ET-CTN.

F. Facilitating coordination of the clinical trial activities and collaborations between the ET-CTN and other NCI-sponsored programs and investigators.
G. Review of clinical trial project proposals, PK/PD, integral, integrated molecular assays, and study requests for use of biospecimens collected in association with ET-CTN trials.
H. Ensuring compliance with FDA requirements for investigational agents, OHRP, and other federal requirements and regulations for research involving human research subjects.
I. Advising awardees concerning mechanisms established by the awardees for QC of therapeutic and diagnostic modalities.
J. Monitoring the progress and performance of the key components of the ET-CTN.
K. Oversight of services provided under contract to support the ET-CTN.
L. Regulatory issues for the protection of patient privacy as it relates to the collection and analysis of molecular characterization and genotyping information.

Additional NCI staff members may be designated to have substantial involvement (e.g., in the role of Project Managers). The NCI Project Scientist(s)/Managers(s) will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications. If such participation is deemed essential, these individuals will seek an NCI waiver according to the NCI procedures for management of conflict of interest.

2. The ET-CTN Director is the NIH/NCI Program Official responsible for the routine scientific and programmatic stewardship of all the awards for the ET-CTN and will be named in the award notice. Some Program Officials may also have substantial programmatic involvement (as Project Scientists/Coordinators). In that case, the individual involved will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications or will seek NCI waiver as stated above. Additional Co-Program Officials may be named in the award notice for some of the key components of the ET-CTN as these Co-Program Directors have major responsibilities in assisting the ET-CTN Director for the scientific and programmatic stewardship of the awards for particular key components of the ET-CTN.

3. Monitoring ET-CTN and site progress. Actions necessary for monitoring may include, but are not limited to, the following: regular communications with the LAO PI(s) and staff; periodic site visits for discussions with LAO research teams; response audits to confirm therapeutic activity reported from a clinical trial; review of audit reports; observation of field data collection and management techniques; fiscal review; review of clinical trial reports submitted to NCI; review of the ET-CTN site annual progress report; and attendance at early phase experimental therapeutic meetings. The NCI retains, as an option, periodic external review of progress.

4. Scientific Liaison: Serving as a resource with respect to other ongoing NCI activities that may be relevant to the ET-CTN research efforts to identify promising new leads, to facilitate compatibility with other NCI research projects, and to avoid unnecessary duplication of effort.

5. Ensuring applicants abide by the Code of Conduct as provided in the ET-CTN guidelines (To Be Provided).

6. The NCI ET-CTN Director and Project Scientist/Senior Clinical Investigator will attend biannual Early Phase Experimental Therapeutic Meetings to discuss relevant scientific information, to discuss progress in the clinical trials, and to discuss the status of newly available

investigational agents and other research opportunities in order to plan future activities. Other NCI staff [e.g., from IDB, Radiation Research Program, and CIP] will attend as needed.

7. CTEP Assistance in Clinical Trial Development: The clinical trial protocol must be a detailed written plan of a clinical experiment mutually acceptable to the LPO and to the CTEP Protocol Review Committee (PRC). Communication at the various stages of protocol development is encouraged as necessary to promote protocol development and implementation. Following review, the NCI staff will provide a consensus review to the LAO and LPO and will address the following issues:
   A. The existence and nature of concurrent clinical trials in the area of research, pointing out possible duplication of effort.
   B. Information, including relevant PK and PD data, concerning investigational agents.
   C. Availability of investigational agents.
   D. The PRC's assessment of the scientific rationale and value of the proposed study, its design, and statistical requirements.
   E. Appropriate inclusion of CTEP Standard Protocol Language for CRADAs and CTAs in the protocol.
   F. The implementation of the study, if indicated.

8. CTEP Review of Clinical Protocols: All early phase experimental therapeutic ET-CTN protocols will be reviewed by the PRC, which meets weekly and is chaired by the Associate Director, CTEP. Ad hoc reviewers, external to NCI, will be utilized when deemed appropriate by the PRC chairperson. Protocols should be preceded by a written LOI from the LPO site declaring interest in conducting a particular study. The LOI mechanism is designed for preliminary review and is recommended to expedite clinical trial protocol development and implementation and to facilitate agreement on study priority and design (for further discussion of these mechanisms, see the DCTD Investigator's Handbook at: http://ctep.cancer.gov/handbook/).The PRC will formally review the LOI. Following the review of the clinical trial protocol by the PRC, the NCI staff will provide the ET-CTN with a consensus review that describes recommended modifications and other suggestions, as appropriate (see the DCTD Investigator's Handbook, for further information regarding protocol review at CTEP). The NCI Project Scientist/CTEP ET-CTN Director will be available to assist the LPO in developing a mutually acceptable protocol, consistent with the research interests, abilities, and strategic plans of the program and of the NCI.

   The major considerations relevant to Protocol Review by CTEP include:
   A. Strength of the scientific rationale supporting the study.
   B. Clinical importance of the question being posed.
   C. Avoidance of unnecessary duplication with other ongoing studies.
   D. Appropriateness of study design.
   E. Consistency with development plans for particular IND agents.
   F. Satisfactory projected accrual rate and follow-up period.
   G. Patient safety.
   H. Compliance with federal regulatory requirements.
   I. Adequacy of data management.
   J. Appropriateness of patient selection, evaluation, assessment of adverse events, response to therapy and follow-up.
   K. Method of monitoring and reporting to NCI to be used, CTMS or CDS.

L. If a proposed clinical trial protocol is disapproved, the specific reasons for lack of approval will be communicated in writing by the NCI Project Scientist to the LAO and LPO as a consensus review within 30 days of protocol receipt by the NCI. NCI will not provide investigational agents or permit expenditure of NCI funds for a clinical trial that has not been approved.

9. CTEP Protocol Amendment Review: Any change to the protocol document subsequent to its approval by CTEP must be submitted in writing for review and approval prior to implementation (See "The Investigator's Handbook", http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf, Part 3: Attachment 9, for further discussion of these procedures).

10. Requests for Use of the ET-CTN Infrastructure Services: The infrastructure of the ET-CTN, including NCI/DCTD-supported contract services, may be used only for ET-CTN trials approved by NCI/DCTD under this Cooperative Agreement. In special circumstances, the LAO may request limited use of certain services (e.g., the RSS, the Oncology Patient Enrollment Network [OPEN] for a related research effort associated with a specific ET-CTN clinical trial that is supported by charitable funds or a related oncology research study funded by another NIH-funded program). These requests must be reviewed and approved by NCI/DCTD via an official written approval by the ET-CTN Director and the Associate Director, CTEP. It is anticipated that only requests that are compatible with and are anticipated to benefit the overall research goals of the ET-CTN would be approved, subject to the availability of ET-CTN resources/funding, since the use of the requested services are funded under the ET-CTN.

11. CTEP Involvement in Clinical Trial Protocol Closure: Protocol closure is primarily the responsibility of the LAO and LPO. The NCI Project Scientist/ET-CTN Director or staff will monitor clinical trial protocol progress and may request protocol closure to further patient accrual if necessary, including the following reasons:
    A. Insufficient accrual rate. In case of insufficient patient accrual per the protocol-specified timelines and/or NCI/DCTD slowly accruing guidelines for trials, inability to meet the scientific aims of the Cooperative Agreement, or noncompliance with the Terms and Conditions of Award, the NCI reserves the right to reduce award budget, withhold support, suspend, or terminate the award.
    B. Accrual goal met.
    C. Poor protocol performance.
    D. Patient safety or regulatory concerns.
    E. Study results are already conclusive.
    F. Emergence of new information that diminishes the scientific importance of the study question.
    G. Lack of availability of the IND agent.
    H. NCI will not provide investigational agents or permit expenditures of NCI funds for a study after requesting closure (except for patients already on-study).
    I. Research misconduct.
    J. Misuse of funds.

12. ET-CTN Meetings: NCI is responsible for the organization of biannual meetings to review ET-CTN progress, establish priorities, and plan future activities. Additional meetings between ET-CTN members and meetings with NCI staff may be held as needed. Relevant responsibilities for meeting organization include:

A. Arranging for appropriate meeting space and accommodations for attendees.
B. Developing and distributing meeting agendas.
C. Ensuring that copies of the Report of Studies (electronic and/or hard copy) are distributed to ET-CTN members and NCI program staff.
D. Preparing summaries as appropriate after each meeting to be sent to ET-CTN members and NCI program staff.

13. NCI/DCTD staff is responsible for maintaining a clear set of national priorities for treatment research, based upon substantial consultation with experts in the field. NCI/DCTD staff with support from the CCCT will assist in coordinating the organization of IDSC meetings under the auspices of the IDSC. NCI/DCTD staff may support ad hoc scientific meetings to achieve consensus on critical clinical problems. The IDSC and ad hoc meetings will be composed of investigators with established expertise in the particular field of interest and will consist primarily of extramural scientists. NCI staff will be responsible for prompt dissemination of the recommendations from these meetings, particularly regarding statements of research priorities from IDSC meetings. The ET-CTN will be encouraged to address these priorities.

14. The NCI/DCTD ET-CTN Director may request and receive budgetary and administrative materials from the ET-CTN on either an ad hoc or routine basis. The NCI/DCTD ET-CTN Director will frequently perform liaison activities concerning budgetary and administrative matters interfacing with the primary Administrators for the ET-CTN Sites.

15. NCI/DCTD staff will take an active role in promoting the timely completion of important studies, for example, by encouraging and facilitating collaboration among the ET-CTN Sites and collaborations with other NCI-supported programs and investigators when appropriate or by assisting in the mobilization of other available and required resources to enhance accrual to and completion of ET-CTN trials.

16. NCI/DCTD staff (i.e., three representatives - one representative from the BRB, the NCIET-CTN Director or his/her designee, and the physician liaison from the IDB/CIB, CDP, or the CIP) are full members on the IDSC. The IDB physician in the related drug area for the IDSC or CIP representative has special responsibilities on the NCI IDSC including developing meeting agendas with the IDSC Co-Chairs, preparing the Consensus Evaluations for proposals evaluated by the committees, and working with the IDSC Co-Chairs on the scientific direction of the committee.

17. Any change in the policies and procedures of the NCI Scientific Steering Committees (SSCs) related to composition of committee membership, conflict of interest, and evaluation/prioritization procedures for ET-CTN clinical trials requires review and approval by the NCI ET-CTN Director, Branch Chief of IDB and the Associate Director, CTEP, DCTD/NCI to ensure that procedures are consistent with the intent of the ET-CTN and the Terms and Conditions of Award under the Cooperative Agreements for all key components of the ET-CTN.

18. The NCI program staff must ensure that U.S. State Department approvals are in place for sites from foreign countries that will be participating in the research even though federal funds will only be used to support the participants from the ET-CTN Sites enrolling patients on study.

1.1.2 Team Science for Project Development

1. Initially, the NCI Senior Scientists will develop collaboratively with the pharmaceutical partners the preliminary list of important development questions.
2. The NCI Senior Scientist will request PTAs, to determine interest in participating on the IDSC drug-specific Project Team. In their PTA, ET-CTN Sites will be asked to provide documentation that they can identify a senior PI or young investigator with mentor to coordinate and conduct the trial from their site.
3. The NCI Senior Scientist will participate in the organization and leadership of the IDSC Project Team (agent, drug development plan), and contribute to the design, implementation, and conduct of drug development plans.

1.1.3 PK/PD, Biomarker Assay, and Molecular Characterization of Patients

ET-CTN sites will comply with all ET-CTN requirements for the PK/PD, biomarker assay, and molecular analyses of clinical samples during the conduct of ET-CTN trials. When scientifically appropriate, ET-CTN Sites may act as a central resource for the PK/PD or molecular analyses specific to an ET-CTN clinical trial. In those cases, the ET-CTN site will:

1. Work with the NCI to provide the scientific and logistical infrastructure to receive, store, and analyze clinical samples from all ET-CTN sites participating in a trial.
2. Be responsible for timely and accurate transmission of data generated from those analyses to the NCI.

1.1.4 Coordination of Clinical Trials and Associated Activities

1. Protocol Development
   A. Any change to the protocol document subsequent to its approval by CTEP must be submitted to CTEP's Protocol Information Office (PIO) in writing for review and approval by CTEP prior to implementation of the change, with the exception of administrative updates. Additional information on the procedures for protocol amendment can be found in the Investigator's Handbook.
   B. Access to agents for Pre-Clinical Testing: For CTEP-sponsored IND agents, CTEP RAB will facilitate transfer of material to investigators with a Materials Transfer Agreement (MTA).
   C. The NCI/DCTD BRC will be constituted in a similar manner to that of the PRC with representation from the extramural oncology community (including experts in pathology, translational science, and statistics) as well as NCI/DCTD representatives and representatives in applicable disease areas. The committee representation will be approved by NCI/DCTD and will be constituted so that ET-CTN representation does not constitute a majority of the committee. Membership will include, but is not limited to the following:
      i. Standing:
         a. Chair: Director, DCTD
         b. Members:
            1. Deputy Director, DCTD
            2. Associate Director, CDP
            3. Associate Director, CTEP
            4. Associate Director, Developmental Therapeutics Program (DTP)
            5. Biomarker biostatistician
            6. Director, Laboratory of Human Toxicology & Pharmacology (LHTP) – contractors will be non-voting
            7. Head, Pharmacodynamic Assay Development and Implementation Section (PADIS) – non-voting

8. Molecular Characterization Laboratory (MoCha) – contractors will be non-voting
9. Chief, Diagnostics Evaluation Branch, CDP – non-voting
10. Chief, Clinical Trials Branch, CIP
11. Chief, RAB, CTEP
12. Chief, IDB, CTEP
13. Associate Branch Chiefs, IDB, CTEP
14. Chief, CIB, CTEP

ii. Ad hoc:
   b. Lead reviewer for clinical trial (IDB or CIB)
   c. Members of standing members' programs, as required
   d. Subject matter experts (may be non-NCI, when required)
   e. Grant program director(s)

iii. Support:
   a. PIO, including medical writer
   b. CTEP Project Manager

2. Correlatives
   A. Correlative and molecular studies embedded in ET-CTN clinical trial studies at the time of initial proposal submission should be appropriately designed as **integral and/or integrated studies** with validated assays or procedures (imaging), robust statistical designs and analysis plans that address specific and important scientific hypotheses. Exploratory studies without a specific hypothesis, validated assay or procedures (Imaging) and robust statistical analysis plan will not be approved. Although optional collection of biospecimens without an approved research plan may be approved for a trial (e.g., adjuvant study), use of the specimen must be approved by CTEP and must be based on studies with specific hypotheses and statistical analysis plans (i.e., biospecimens cannot be "reserved" for future unspecified research without a subsequent study proposal being reviewed and approved).
   B. Correlative and molecular studies requesting use of biospecimens from any ET-CTN clinical trial that **has not** yet reported out primary results is evaluated by CTEP's PRC (usually as an amendment during the course of the conduct of the study). At CTEP's discretion, depending on the timing of the request, the study may be sent for evaluation to an NCI/DCTD-approved ET-CTN Correlative Science Committee.
   C. All correlative and molecular studies requesting use of biospecimens from any ET-CTN clinical trial that **has** reported out primary results (i.e., request for use of "banked" biospecimens) are reviewed by CTEP's PRC or sent by CTEP for evaluation to an NCI/DCTD-approved DCTD Biomarker Review Committee (BRC).
   D. It is anticipated that all requests for use of "banked" biospecimens collected in association with any ET-CTN clinical trial (regardless of funding source) will be submitted to a central NCI/DCTD BRC to assess the appropriateness of the request for use of these unique resources that are linked to annotated clinical trial data. This includes outcome data, as well as determining, with the ET-CTN Sites based on its biospecimen inventory and the status of the clinical trial data, whether the request could be addressed. If the central NCI/DCTD BRC determines that the request is appropriate, the request will be sent to NCI/CTEP's PIO for evaluation via CTEP's PRC and NCI/DCTD-approved BRC. Studies requesting use of "banked" biospecimens should be appropriately designed with validated molecular assays or imaging procedures, robust statistical designs and analysis plans that address specific and important scientific hypotheses (and with the statistician named as part of the study proposal on its

title page). Studies for integral and integrated assays will receive the highest priority for analysis.

E. All correlative, molecular, and imaging studies require CTEP review and approval by one of the procedures described above regardless of the number of patient specimens requested. It is anticipated that requests for a small number of specimens that do not constitute an important subset (e.g., specimens from only patients with a particular outcome when the outcome was a rare event) and do not require approval and/or comment by a CTEP collaborator will undergo an expedited review/approval process; however, review and approval are required (there are no "file-only" studies).

F. All requests for biospecimens collected in conjunction with or tied to an ET-CTN trial that are "banked" must undergo review and approval even if the collection or storage of specimens was funded from sources outside the ET-CTN. An ET-CTN clinical trial supported by the NCI/DCTD under these Terms and Conditions of Award requires review under a process approved by NCI/DCTD unless a specific exemption to the review policy is granted by NCI/DCTD. This requirement reflects NCI's scientific interest and a substantial public policy interest in assuring biospecimen collections that are tied to publicly funded ET-CTN trials are made available to the general research community through an NCI-approved review process for meritorious use.

G. Banked biospecimens in NCI-funded or other tumor banks tied to ET-CTN trials cannot be released without an approval letter from NCI/DCTD authorizing release for a specific research proposal that has been approved by the procedures described above. There are **no** exceptions to this policy.

3. Data Management

A. Data Management and Analysis Review: Biometric Research Branch staff will review mechanisms established for data management and analysis. When deemed appropriate, the NCI ET-CTN Director or staff will make recommendations to ensure that data collection and management procedures are adequate for QC and analysis and as simple as appropriate in order to encourage maximum participation of physicians entering patients and to avoid unnecessary expense. The NCI will have access to all data although they remain the property of the awardee institution. Data must be available for external monitoring as required by NCI's agreement with the FDA relative to the NCI's responsibility as drug sponsor.

B. Data and Safety Monitoring Plans: The NCI ET-CTN Director, assisted by the BRB staff, will assess compliance with NCI and NIH established policies on Data and Safety Monitoring Plans. The NCI Project Scientist must review and approve the DSM Plan.

C. Access to and Monitoring of Data: The NCI will have access to all data generated under this cooperative agreement and may periodically review the data. Data must be available for external monitoring as required by NCI's Drug Master File Agreement with the FDA relative to the responsibility of CTEP as an IND sponsor. The awardee will retain custody and primary rights to the data consistent with current HHS, PHS, and NIH policies. The awardee will comply with the data access provisions of applicable CTAs and CRADAs, and when these agreements are in place the pharmaceutical collaborator will have complete access to the data for any and all regulatory filings.

4. Regulatory

A. CTEP sponsorship of IND Applications: The NCI ET-CTN Director and Project Scientist, assisted by the Chief of the RAB, CTEP, and staff will advise investigators of specific requirements and changes in requirements concerning IND issues or IDE issues that the FDA

may mandate. Investigators performing trials under cooperative agreements will be expected, in cooperation with CTEP, to comply with all FDA requirements for investigational agents and assays.

B. CTEP Review of Federally Mandated Regulatory Requirements: The CTMB and RAB, through the NCI ET-CTN Director and Project Scientist, will advise the program regarding mechanisms to meet FDA and OHRP requirements for the protection of human subjects by program institutions.

C. IDB and CIB staff will provide updated information to the ET-CTN Sites on the efficacy and adverse events associated with new investigational agents supplied to ET-CTN Site members under a CTEP-sponsored IND. IDB staff will advise the ET-CTN Sites of potential agents/interventions that will be relevant to new avenues of cancer therapy.
These requests may also require approval or review/comment by a CTEP collaborator if the study is/was conducted under a CTEP binding collaborating agreement per requirements of the CTEP IP option (see information on the CTEP IP Option available at: http://ctep.cancer.gov/industryCollaborations2/default.htm.

D. The protocol document must be reviewed and approved by NCI/DCTD prior to distribution by a ET-CTN Site to other sites for NCI Central IRB review or local IRB review and trial activation (i.e., opening the study to patient enrollment after approval of the study by at least the CIRB or one IRB).
   i. All approved adult study protocols require approval by the NCI CIRB **after** approval of the protocol document by CTEP; however, distribution of the trial may proceed to sites using other IRBs **prior** to final CIRB approval.
   ii. Any changes/modifications requested by the NCI CIRB at the time of its initial review may require an amendment to the study after distribution if CTEP believes any of the requested changes/modifications should be in the master protocol document (either in the informed consent or in other sections of the protocol document).
   iii. Minor changes in the informed consent document may be limited to the approved CIRB version of the informed consent document for its sites only. After the trial is activated, all protocol amendments submitted on the trial require NCI CIRB approval prior to final approval of the amendment by CTEP.
   iv. In select cases, phase 2 trials may be required by NCI/DCTD to be reviewed by the NCI CIRB, especially those phase 2 studies that may be opened widely across the entire ET-CTN.

5. Data Sharing
Requests for use of clinical data only from an ET-CTN clinical trial are subject to the CTEP-approved data-sharing policy of the ET-CTN Site that leads/led the trial. These requests may be subject to review and approval by a Data Analysis Committee (DAC) prior to release of "publically" available information.

6. Research Pharmacy Management
NCI staff will monitor these activities.

7. Career Development and Mentored Training of Junior Investigators
NCI staff will monitor these activities.

8. Performance

The NCI ET-CTN Director will monitor and review annual progress reports. Performance of each ET-CTN site will be reviewed on the basis of the information provided at the semi-annual and other meetings, in the annual progress reports, and in the CDS reports submitted to CTEP for each of the clinical trials. Insufficient patient accrual or progress, or noncompliance with the terms of award, including these Terms and Conditions of Award, may result in a reduction of budget, withholding of support, suspension or termination of the award.

1.IV.1.B.3. Collaborative Responsibilities

The cooperative agreement awardee shall, with CTEP assistance as described in the above terms for the NCI staff responsibilities, develop appropriate early phase experimental therapeutic clinical trial protocols. The protocols must be acceptable to the CTEP PRC.

PIs of the ET-CTN awards, NCI ET-CTN Director, and CTEP Senior Investigators will be members of the ET-CTN. ET-CTN Sites will become members of the ET-CTN upon notice of grant award. ET-CTN Sites will be expected to participate as active team members on the drug development project teams. They will meet quarterly to review studies performed under the award and more often to participate on and provide input for the IDSC, with respect to the development of drug development plans.

In general, all ET-CTN Sites will be expected to participate in all ET-CTN protocols. It is anticipated that some studies will be initiated as limited Institutional studies, which may require expansion to all ET-CTN Sites in order to meet accrual targets. Awardees may collaborate to perform specific pharmacologic, correlative, molecular or imaging studies. For example, to minimize duplication of effort in assay validation and QA procedures, researchers based at one ET-CTN Site may perform assays and correlative studies on biopsies provided by another ET-CTN Site. CTEP scientists will assist investigators in the ongoing coordination required for such cross-award collaborations.

Areas of Joint Responsibility include:

1. **Scientific Leadership**
   A. ET-CTN members in conjunction with NCI staff will collaborate cooperatively to achieve ET-CTN objectives outlined previously.
   B. Applicants must abide by the Code of Conduct as provided in the ET-CTN guidelines (To Be Provided).
   C. The ET-CTN Sites will be involved in developing collaborations with other ET-CTN Sites as well as other NCI-sponsored programs and investigators (e.g., SPOREs, Cancer Centers, R01/P01 investigators) to augment and enhance the drug development plans and research productivity on clinical trials conducted in the ET-CTN. The LAO is responsible for participating in the collective management of the ET-CTN, including participation in appropriate ET-CTN activities and initiatives (e.g., NCI CIRB, IDSC, and NCI Support Services) by making recommendations on NCI drug development.
   D. The LPO, working with the LAO, will collaborate with other ET-CTN Sites to name co-PIs for studies that the LPO leads to augment accrual via collaboration on its ET-CTN trials.
   E. The NCI will collaborate and cooperate with the ET-CTN Sites to assure collective management of the ET-CTN as needed. To achieve this goal, the PI of the LAO of the ET-CTN Site will participate in the IDSC. The IDSC is composed of key NCI/DCTD staff (Division Director DCTD, Associate Director CTEP, Chief and Associate Chiefs of the IDB CTEP, CDP Associate Director, and CIP Branch Chief) and other representatives. The IDSC Coordination

Team is made up of core elected and appointed IDSC members who set the agenda for the IDSC. This team will be Co-Chaired by elected early phase experimental therapeutic PIs, in collaboration with NCI representatives and other appointed members. The Coordination Team and the IDSC will meet regularly to discuss issues of drug development. It is anticipated that the IDSC will meet on at least a quarterly basis in-person. Additional representatives from the ET-CTN may be invited to participate in meetings depending on the issues to be discussed.

F. Arbitration Process
   i. Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and/or the NIH may be brought to dispute resolution, except for areas of dispute that are already addressed by the appeal process within the Terms and Conditions of Award for decisions regarding approval of study proposals and the types of studies supported by the ET-CTN as described in Part 1 – Section IV.E. of these Guidelines.
   ii. Any disagreement that may arise on scientific/programmatic matters (within the scope of the award); excluding patient safety issues or regulatory compliance, between award recipients and/or the NCI may be brought to arbitration. An Arbitration Panel will be convened to review the issue and recommend an appropriate course of action to the Director, DCTD.
   iii. The panel will be composed of the following three members: a designee of the awardee(s), one NCI designee (if appropriate), and a third designee with expertise in the relevant area who is chosen by the other two parties. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulations 42 CFR Part 50, Subpart D and HHS regulations 45 CFR Part 16. The Arbitration Panel will be convened to review the proposed resolution and recommend an appropriate course of action to the Director, DCTD. The DCTD Director will determine the final course of action, unless the involved parties agree to the proposed resolution. All decisions by the DCTD Director are final and binding.
   iv. The LAO should arbitrate disputes with its subcontractors internally. The LAO should define an arbitration process and corrective action plan to address disputes. The LAO arbitration process should be described in the application. NCI, as sponsor, may provide non-binding input if requested.
   v. For other scientific and programmatic matters that are not covered by the appeals process, a Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the ET-CTN representatives on the ET-CTN Coordination Team chosen by them without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two parties; in the case of individual disagreement, the first member may be chosen by the individual awardee.
   vi. This appeal process is only for disagreements related to scientific merit decisions made on study proposals for the ET-CTN or the programmatic definition of study types supported under the ET-CTN.
   vii. The appeals process for decisions related to study proposals supported under the ET-CTN (including both intervention and non-intervention studies) is described below.
      a. For ET-CTN clinical trials evaluated by the CTEP PRC for drug/disease areas that are not approved for development based on scientific merit, the LAO or LPO may "appeal" the decision to the DCTD Director, if the LAO or LPO believes that there

were factual errors in the evaluation that led to the disapproval. If the DCTD Director agrees with the appeal request by the LAO or LPO, the DCTD Director will instruct CTEP's PRC to re-evaluate the study proposal. The result of the re-evaluation will be communicated to the DCTD Director, and a final decision will be rendered.

b. For early phase LOI proposals evaluated by NCI/CTEP's PRC for trial proposals that **would be conducted under CTEP IND**, the LAO or LPO may appeal an LOI not approved for development based on scientific merit by requesting that the IDSC review the LOI and make recommendations. The result of the review of the LOI by the IDSC will be considered by the PRC. The PRC will make a final binding decision.

c. ET-CTN non-intervention studies (i.e., studies that request use of biospecimens collected in association with an ET-CTN trial) will be reviewed by NCI/CTEP's PRC or evaluated by an NCI/DCTD-approved ET-CTN BRC. The LAO or LPO may appeal a study proposal not approved for development based on scientific merit to the DCTD Director, if the LAO or LPO believes that there were factual errors in the review that led to the disapproval. If the DCTD Director agrees with the appeal by the LAO/LPO, the DCTD Director will instruct CTEP's PRC or the NCI/DCTD-approved ET-CTN BRC to re-evaluate the study proposal. The result of the re-evaluation will be communicated to the DCTD Director, and a final decision will be rendered.

d. The Associate Director, NCI/CTEP makes decisions regarding the interpretation of the types of studies funded under the ET-CTN in consultation with the IDB Chief and NCI ET-CTN Director. The LAO may appeal this decision to the DCTD Director for a particular study, if the LAO believes the type of study is within the scope of the ET-CTN as described in these Guidelines. If the DCTD Director agrees with the appeal by the LAO or LPO, the DCTD Director will direct NCI/DCTD to consider the proposal under the appropriate evaluation or review procedures for the ET-CTN as described in these Guidelines.

2. **Team Science for Project Development**
   A. The NCI and the IDSC Project Team will work together cooperatively to finalize important drug development questions and the drug development plan.
   B. The list of important questions and the development plan will be sent to the full IDSC for comment prior to implementation.
   C. Members of the IDSC Project Team will be encouraged to submit individual LOIs to address each important question.
   D. ET-CTN Sites are expected to lead and/or participate in multi-disciplinary scientific and general aspects of collaboration on study development.
   E. The ET-CTN will accomplish its objectives by forming multi-institutional, multi-disciplinary project teams to define drug development with the support of the IDSC.
   F. **When a project team forms for a specific agent, at the outset, the LAO needs to provide documentation describing approach and recommendations to team science authorship as outlined in major medical journals.**

3. **PK/PD, Biomarker Assays, and Molecular Characterization**
   ET-CTN sites will comply with all ET-CTN requirements for the PK/PD and molecular analyses of clinical specimens during the conduct of ET-CTN trials. When scientifically appropriate, ET-CTN Sites may act as a central resource for the validated PK/PD, biomarker assays or molecular analyses specific to an ET-CTN clinical trial. In those cases, the ET-CTN site will:

A. Work with the NCI to provide the scientific and logistical infrastructure to receive, store, and analyze clinical samples from all ET-CTN sites participating in trial.
B. Be responsible for timely and accurate transmission of data generated from those analyses to the NCI.

4. **Coordination of Clinical Trials and Associated Activities**
   A. Protocol Development
      i. Because of the significant resource, regulatory, and general administrative issues involved in ET-CTN key component activities and to ensure required compliance with other federal regulations and federal agencies, the ET-CTN Sites and other key components of the ET-CTN should collaborate closely with NCI/DCTD staff.
      ii. This collaboration should occur early in the development of trials, general research strategies, and new initiatives.
      iii. When new avenues of cancer therapy involving investigational drugs are pursued, the trial should be designed such that the clinical information obtained should be acceptable to the FDA for inclusion in a potential licensing application.
      iv. NCI/DCTD staff and the ET-CTN Site should work collaboratively to develop protocols meeting GCP standards.
      v. All parties (ET-CTN Site, NCI/DCTD staff, and company collaborators) should be involved in any conference calls and/or meetings involving the FDA during the development and conduct of any approved ET-CTN trial with licensing potential, regardless of whether the study is being conducted under CTEP IND to ensure that all sponsors are involved in discussion regarding the trial.
      vi. Both the ET-CTN Sites and NCI/DCTD share the responsibility to ensure that study proposals are reviewed/evaluated, protocols developed, and trials activated in a timely manner per the timelines established and approved by the OEWG, including target and absolute deadlines for opening trials to patient enrollment. A description of the OEWG process, requirements, and required timelines are available at: http://ctep.cancer.gov/SpotlightOn/OEWG.htm.

5. Correlatives
   The NCI, DCTD, CTEP and the ET-CTN will work cooperatively together in a collaborative fashion to prioritize, review, and perform *in vitro* molecular assays and imaging studies in the context of early experimental therapeutics trials.

6. Data Management
   A. Accrual Credit: All accrual credit requests shall be discussed and agreed upon with the NCI ET-CTN Director prior to study initiation and documented in writing or electronically. Suitable subjects for accrual credit include but are not limited to:
      i. Enhanced enrollment to early experimental therapeutic trials based on race/ethnicity.
      ii. Participants screened for trials conducted by the ET-CTN.
      iii. Recruitment to high complexity clinical trials.
      iv. Recruitment to trials for rare or orphan cancers.
   B. Both the ET-CTN Sites and NCI/DCTD share responsibility to collaborate on initiatives to promote accrual to ET-CTN trials.
   C. The ET-CTN Sites are required to use specific ET-CTN common services and tools, including but not limited to those listed below, for all ET-CTN trials in order for the trials to be approved for activation:

i. ET-CTN Common Data Management System for data collection.
ii. ET-CTN System for tracking biospecimen collection from ET-CTN trials (in development).
iii. ET-CTN OPEN via the CTSU.
iv. ET-CTN RSS via the CTSU.
v. Establish and maintain site, investigator and associate rosters with the CTSU.NCI CIRB Review for studies as required under these Guidelines.

7. Legacy Studies
Legacy studies supported by the ET-CTN will be conducted under the same ET-CTN Terms and Conditions of Award as are those studies that commence under the ET-CTN. Hence, the awardees of any of the key components of the ET-CTN are bound by the Terms and Conditions of their Award under the ET-CTN when working on legacy studies that are supported by the ET-CTN.

8. QA/QC of Early Phase Clinical Trials
QA/QC is a complex topic spanning the entire range of diagnostic and therapeutic modalities employed by the program. QA/QC Programs are inherently linked. The CTEP CTMB provides direct oversight of CTEP-sponsored QA/QC programs. The ET-CTN is responsible for complying with implemented mechanisms to assure the accuracy and reliability of its clinical trials data. Key items that should be addressed concerning QA/QC procedures include:
   A Institutional performance evaluations. Performance factors to be considered include:
      i. Accrual of adequate number of eligible patients onto trials.
      ii. Timely, accurate submission of required data.
      iii. Rigorous adherence to clinical trial protocol requirements.
      iv. Participation in study development and in timely publication of study findings.
   B Procedures will be in place for putting ET-CTN sites on probation for inadequate performance and for removing such institutions from the early experimental therapeutics program if performance is not adequate by the end of the probationary period or at any time that the institution (or participating site) does not meet established ET-CTN standards.
   C Educational functions that address data collection, data management, and overall data quality. These aspects include, but are not limited to, the following elements:
      i. Training may be provided by CTMS for new CRAs in the ET-CTN's data submission policies and ongoing training for all CRAs concerning changes to program procedures and instructions for data submission in new protocols.
      ii. Instruction for LPOs on their responsibilities for study monitoring.
      iii. Instruction for Integrated Components and AO PIs and members on their responsibilities in complying with the ET-CTN's SOPs and Federal regulations at their institution.
      iv. Training/guidance should be provided to all participants on how to comply with NCI/NIH policies and procedures (e.g., Ethics, Conflict of Interest, etc.) in addition to the policies and procedures of other governmental agencies important to the conduct of clinical trials (e.g., OHRP, FDA).
   D Procedures for central review of major elements that impact the outcome of clinical trials. This will include central review of claimed responses and adequacy of imaging studies submitted by ET-CTN Sites, central review of submitted data with determination of protocol compliance in dose administration and dosage modification, and additional review as necessary.

E The CTMB, CTEP, NCI is responsible for monitoring and oversight of the ET-CTN QA/QC programs. The CTMS (currently awarded as a contract to Theradex®) administers the early phase experimental therapeutic data management and auditing functions on behalf of CTMB.

i. Onsite auditing of ET-CTN Sites will occur approximately three times/year for studies assigned to CTMS monitoring, with the timing of audits to be based in part on ET-CTN Site accrual. The onsite audit will address issues of data verification, protocol compliance, compliance with regulatory requirements for the protection of human subjects and investigational agent accountability. For ET-CTN studies assigned to be CDS monitored, audits will be conducted at least once every 3 years or more; more frequently if warranted by accrual. NCI/CTEP reserves the right to conduct an onsite audit at any time.

ii. The LAO's Coordination of Clinical Trials and Associated Activities component will be responsible for logistical coordination and ensuring follow-up of audit findings.

iii. Any serious problems with data verification or compliance with Federal regulations must be reported to the CTMB immediately. Otherwise, written reports by CTMS must be submitted within 4 weeks of each audit to CTMB.

iv. The LAO's Coordination of Clinical Trials and Associated Activities component will be responsible for coordinating development of and compliance with Corrective and Preventive Action Plan (CAPA) in response to audits. If the NCI determines that any component of an ET-CTN Site failed to adequately comply with NCI guidelines for conduct of clinical trials, accrual of new patients to ET-CTN protocols at the ET-CTN Sites shall be suspended immediately upon notice of the NCI determination. The suspension will remain in effect until the LAO conducts the required audit and NCI accepts the audit report or CAPA.

v. The LAO will be responsible for notifying any affected Integrated Component and/or AO of the suspension. During the suspension period, no funds from this award may be provided to the ET-CTN Sites for new accruals, and no charges to the award for new accruals will be permitted.

vi. Any data irregularities identified through QC procedures at an ET-CTN Participating Institution or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB, CTEP, NCI. For data irregularities:

a. The CTMB must be notified immediately by telephone or email of any findings suspicious and/or suggestive of intentional misrepresentation of data and or disregard for regulatory safeguards for any of the three (regulatory, pharmacy, and patient care) components of an audit.

b. Any data irregularities identified through other QC procedures suspicious and/or suggestive of intentional misrepresentation of data must be immediately reported to CTMB.

c. It is the responsibility of the LAO to immediately notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in the ET-CTN clinical trials.

d. The irregularity/misrepresentation does not need to be proven; a reasonable level of suspicion suffices for CTEP CTMB notification.

e. Involved individual(s) and/or institutions should follow their own institutional misconduct procedures in these matters.

f. Clinical Trials Operations – Conduct of Clinical Trials & Data Management: The ET-CTN Sites should have a clearly articulated process for prioritizing ET-CTN trials at their institutions. Investigators at ET-CTN Sites form the cornerstone of the research programs for the ET-CTN and must perform at a high level through submission of accurate and timely clinical data, as well as ancillary materials necessary to support the ET-CTN (e.g., tumor specimens, imaging studies, pathology slides). The PI(s) at each ET-CTN Site is responsible for the performance at their institution which includes timely submission of data and for assuring adherence to ET-CTN, NCI, OHRP, and FDA policies and procedures. International standards for the conduct of clinical trials (ICH E6: Good Clinical Practices at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf) should be observed and followed by all research personnel involved in conducting the study.

It is the responsibility of the PI(s) at the site to ensure that all investigators at the ET-CTN Sites understand the procedures for data submission for each ET-CTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave. This includes:

1. All ET-CTN Sites must utilize Medidata Rave as the common electronic data capture system.
2. Patients must be registered and treated at an approved ET-CTN Site.
3. Research staff at the Participating Institution will require an Identity and Access Management (IAM) password to access Medidata Rave and other CTEP systems. See: http://ctep.cancer.gov/branches/pmb/associate_registration.htm.
4. Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks.
5. All patients who are consented to ET-CTN studies (including patients who are found to be screen failures) will be registered prospectively using OPEN.
6. The submitted data will undergo a centralized clinical QA review at CTMS. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ET-CTN to resolve.
7. A protocol-specific eligibility electronic Case Report Form (eCRF) will be completed by the enrolling institution and electronically transmitted to CTMS via the OPEN.
8. The eligibility eCRF may include collection of molecular profiling/genotyping information which will be stored and maintained by Medidata Rave and may be used to identify additional protocols that the patient may be eligible for enrollment. Electronic Case Report Forms will be built in Medidata Rave by the CTMS and available to all ET-CTN sites at the time of protocol activation. eCRFs will include but may not be limited to the following:
    a. Eligibility and Enrollment
    b. Prior therapies
    c. Concomitant Medications/Interventions
    d. Baseline Medical History and Physical Exam
    e. Baseline Symptoms
    f. Baseline and Follow-up Extent of Disease
    g. Course Initiation
    h. Study Drug Administration
    i. Adverse Events

j. Course Assessment
k. Laboratory Evaluations
l. PK/PD
m. Correlative (biomarker, molecular and imaging) Studies

9. End of Study CRF: to be completed by the PI to include the recommended phase 2 dose (RP2D), a description of any dose-limiting toxicities. CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant. Customized eCRFs will be included when appropriate to meet unique study requirements. The LPO PI is encouraged to review the eCRFs working closely with CTMS to ensure prospectively that all required items are appropriate captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

F The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due. Institutions with data greater than 20% past due at the end of the quarter will be put on probation. If delinquent data issues persist and are not resolved at the time of the following quarterly assessment, registration privileges to the ET-CTN will be suspended until all delinquent data are submitted and a corrective action plan for ensuring timely data submission is submitted and approved by CTMS and the NCI ET-CTN Director.QA and Onsite Auditing:

i. Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and human subjects who participate in research studies. The following should be adhered to in the ET-CTN:
   a. Good Clinical Practice (GCP) is an International ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials results that involve the participation of human subjects. Information on GCP standards in FDA-regulated Clinical Trials is provided at: http://www.fda.gov/oc/gcp/default.htm.
   b. Ensuring adequate safeguards is particularly important when conducting early phase clinical trials where the mechanism of action of the agent and/or adverse event profile for the agent may be less understood.

ii. ET-CTN sites should strive to comply with this standard to the greatest degree possible since it provides public assurance that the rights, safety, and well-being of trial patients/participants are protected, and that the data generated from the clinical trial are credible. The integrity of the clinical trial is a function of the entire process of data collection and analysis. Vigilance to detect honest errors, whether systematic or random, as well as data fabrication and/or falsification are especially important when conducting clinical trials since independent replication of most trials is not feasible. Goals of the QA Program should be:
   a. To prevent problems.
   b. To select responsible investigators and research staff.
   c. To detect problems by implementing routine monitoring procedures. The system should make detection of both random errors and systematic errors feasible during the course of data collection. Procedures for data audit and statistical methods should be implemented to detect certain types of problems, but purposeful fraud may be very difficult to detect.

d. To take appropriate action in a timely and effective manner. It should be recognized that some errors will remain undetected and uncorrected regardless of the QC, editing, and auditing procedures in place.
e. To serve as a valuable educational vehicle. The onsite visit team should use the opportunity to share with the local staff GCP techniques and data management and QC systems that have been successfully implemented at other institutions. The local staff can use the results of the onsite audit to identify operational areas where improvements could be made.

iii. Data from Medidata Rave and AdEERS is reviewed by the CTMS on an ongoing basis as data is received. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials. To assist the CTEP in fulfilling its regulatory responsibilities as an IND sponsor and to assure protocol compliance and source data verification, the CTMS contractor performs the Audits of ET-CTN participating institutions:
   a. Audit will closely follow the policies outlined in the section 16 of the Investigator's Handbook (see: http://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf and the CTMB Guidelines: http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm. Representatives from the CTMS will, depending on enrollment, conduct two data audits per year and one annual site visit per year to each of the ET-CTN participating institutions. Audits shall be scheduled at a minimum of 4 weeks in advance of the anticipated audit date. The minimum requirements for the initial audit or subsequent audits will include a meeting between the Contractor Physician/CRC or CRA and the investigator to review his/her understanding of FDA regulations and DCTD policies/procedures for conducting investigational agent trials. These include:
      1. FDA regulations concerning GCP, IRB obligations, Informed Consent Regulations and Obligations of Sponsors, Monitors, and Investigators.
      2. DCTD, CTEP requirements for submission and review and approval of protocol and amendments prior to clinical trial activation at an institution.
      3. DCTD's Expedited Adverse Event Reporting Requirements via AdEERS and procedures and the use of DCTD's CTAE4.0 or subsequent versions.
      4. NCI DARFs and pharmacy procedures for proper drug accountability.
      5. Review of DCTD required protocol patient data capture procedures and QC review of submitted data.
      6. Review of the scope of the investigator's research efforts and the adequacy of facilities for conducting the research. The Physician/CRC/CRA monitor shall collect the institution's laboratory normal values.
      7. Review of regulatory procedures and documentation of approval for:
         a. Verification of initial IRB approval for each protocol and all amendments, as well as the required continuing annual IRB approvals and safety reports.
         b. Review of the local consent form to assure that it is consistent with the informed consent form approved by the CTEP, PRC. Also, a review shall be conducted to determine if the consent form being used is the current IRB approved version.

b. The data verification audit encompasses the submitted patient data component of the audit. The CTMS auditor will review protocol compliance to assure patient cases are treated in accordance with protocol specifications and that data have not been omitted from submission.
c. The Patient Case Review will include:
    1. Comparison of source documents to the protocol patient data capture submissions electronically.
    2. For all patient cases reviewed, verification of the presence of an IRB-approved, properly signed and dated informed consent form.
    3. Verification of patient eligibility.
    4. Assessment of compliance with protocol treatment requirements, including the presence of proper documentation of treatment administration and adherence to dose/treatment modification requirements.
    5. Verification that the response is assessed in accordance with the criteria described in the protocol.
    6. Review of patient records to ensure the timely reporting of adverse events requiring expedited reporting via AdEERS. The CTMB is to be promptly notified of any unreported adverse event during the audit that required expedited reporting.
    7. Verification that protocol-required parameters (labs, exams, scans, etc.) were obtained in accordance with the protocol.
    8. A review of the NCI Investigational Drug Accountability Record Forms (DARFs) and of procedures for storage, distribution, and the security of investigational agents to include:
        a. A comparison of actual shelf inventory (vial count) versus the NCI DARFs.
        b. For the patient cases selected for audit, a comparison of agent dispensed as recorded on the NCI DARFs, versus that recorded as administered in patient source records.
        c. A comparison of the NCI DARFs with the protocol registration listing along with dates to assure all patients who received investigational agents were actually registered on the specified protocol.

iv. ET-CTN sites are encouraged to participate in a pilot project involving remote electronic data audits. The pilot project involves conducting the twice per year data audits by CTMS staff remotely accessing the patient's electronic medical records (EMR). Such an approach leverages the capabilities of the EMR and Electronic Data Capture (EDC) and represents a cost-efficient approach for ensuring the integrity of clinical data. The annual site visits, which include review of the pharmacy and IRB records, would remain an onsite process. ET-CTN sites must be willing to allow remote access to patient records and have the ability within their EMR system to segregate and allow access to only those records pertaining to the patients enrolled on ET-CTN studies that are requested by CTMS for review.

9. Regulatory

For foreign sites or sites with foreign collaborators, ET-CTN Sites are required to have a binding collaborative agreement in place with the international clinical trial organization that addresses the major components of clinical trial conducted by the international organization. This is to

ensure that the conduct is consistent with all appropriate federal and other appropriate regulations for the clinical research trial. This agreement must be reviewed and approved by the ET-CTN Director in consultation with the Associate Director of CTEP and the Chief, CTEP RAB. All appropriate U.S. State Department approvals must be in place for countries that will be participating in the research as well as other appropriate approvals (e.g., company partner approvals for trials being conducted under an NCI/DCTD binding collaborative agreement or CRADA).

1.IV.2. Reporting

When multiple years are involved, awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590 or RPPR) annually and financial statements as required in the *NIH Grants Policy Statement*.

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000. See the NIH Grants Policy Statement for additional information on this reporting requirement.

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 (http://grants.nih.gov/grants/funding/2590/2590.htm), annually, and financial statements as required in the NIH Grants Policy Statement. Performance of the program in developing new LOIs and protocols should be discussed, as should the performance of AOs participating in studies and the performance of reference laboratories. An update on clinical trials that were approved, activated, closed, and/or completed during the relevant budget period should be discussed in the progress summary and once a quarter in an abbreviated tabular format. Plans pertaining to clinical trial activities for the next budget period should be addressed as well.

Clinical trials reporting requirements will be in agreement with FDA regulations and NCI procedures. Interim reports of each activated and ongoing clinical trial should be prepared for each biannual meeting and shall include specific data on patient/participant accrual as well as detailed reports of treatment-associated morbidity. CTMS reporting is required every 2 weeks. Information pertaining to CTMS monitoring is accessible at: http://www.theradex.com/CTMS/Default.aspx. Quarterly accrual reports must be provided as appropriate to CTEP for all active trials through the NCI's CDS. Instructions and Guidelines for CDS reporting are at: https://cdsweb.nci.nih.gov/cdsweb/loginPage.do. The use of the tables in the Resources section of this FOA are strongly encouraged for reporting progress in the required annual progress report.

1.IV.3. Additional Information

1.IV.3.A. Requests for Use of Clinical Data

Requests for use of clinical data only from an ET-CTN clinical trial is subject to the CTEP-approved data-sharing policy of the LAO. These requests may be subject to review and approval by NCI Program staff (or "CTEP collaborator" instead) if the study is/was conducted under a CTEP binding collaborating agreement per requirements of the CTEP IP option (see information on the CTEP IP Option at: http://ctep.cancer.gov/industryCollaborations2/default.htm).

Some or all of this data may be exempt from Freedom of Information Act (FOIA) requests under exemption 6, U.S.C. § 552 (b) (6) which "permits the government to withhold all information about individuals in "personnel and medical files and similar files" when the disclosure of such information "would constitute a clearly unwarranted invasion of personal privacy. Individuals do not waive their privacy rights merely by signing a document that states that information may be released to third parties under the FOIA.As one court has observed, such a statement is not a waiver of the right to confidentiality, it is merely a warning by the agency and corresponding acknowledgment by the signers "that the information they were providing could be subject to release".

1.IV.3.B. Protocol LOI Review/Approval

Evaluation/Review Outcome: In general, CTEP's PRC discusses the submitted LOI with all assigned reviewers and committee members and makes a decision on the study proposal from one of the 3 options provided below. A similar process is followed for CTEP's PRC review of non-intervention study proposals (i.e., correlative science studies requesting use of biospecimens collected in association with an ET-CTN trial).

Approved as written or with recommendations – The investigators are requested to give serious consideration to any recommendation included in the consensus review/evaluation but they are not obligated to amend the study proposal. If changes are made prior to activation of the study, the investigators must send CTEP a revision for review that details any changes in the previous CTEP-approved document.

Pending Approval is given initially for studies requiring review/approval by a CTEP collaborator (e.g., collaborator providing investigational agent for the trial) and if/when the CTEP collaborator gives official approval, CTEP issues a final full approval for the study with or without recommendations. On occasion, an approval may come with a required modification specified in the approval letter and/or attached Consensus Evaluation/Consensus Review that will need to be incorporated into the study proposal at the time of protocol review. This is done for minor modifications so that the trial proposal does not need to go back as a pending when the modification is straightforward.

On Hold -The CTEP PRC has significant questions about the proposed study. The proposed study can be approved if the investigators satisfactorily address the concerns included in the written consensus review/evaluation adequately (i.e., comments requiring a response).

Disapproved – In the judgment of CTEP's PRC, the study cannot be approved. All PTA study proposals that are prioritized by the IDSC NCI or an NCI/DCTD-approved ET-CTN BRC must undergo review by CTEP before final approval is given. This is done to ensure significant safety, feasibility, and regulatory issues are adequately addressed, including ensuring that there are adequate resources available for the study

proposal or trial given the resource allocation constraints for the disease area, and to prevent duplication. However, it is expected that this final review/approval by CTEP can be accomplished in a routine manner (approximately 2weeks) in most cases as designated NCI/DCTD staff participate as full members on the IDSC or the NCI/DCTD-approved ET-CTN BRC. Significant issues in these areas are incorporated into the evaluation/prioritization discussion.

Any approved ET-CTN early phase trial is submitted to FDA for comment. Any approved ET-CTN LOI with an investigational device/biomarker may also be submitted to FDA for comment even if the study is not identified as being specifically designed for a licensing indication for an agent or device.

1.IV.2.A. Protocol Development Review/Approval and Amendment Review/Approval

The protocol document must be reviewed and approved by NCI/DCTD prior to distribution by an ET-CTN site to other sites for NCI CIRB review or local IRB review and trial activation (i.e., opening the study to patient enrollment after approval of the study by at least the CIRB or one IRB). All approved adult study protocols also require approval by the NCI Adult CIRB **after** approval of the protocol document by CTEP. However, distribution of the trial may proceed to sites using other IRBs **prior** to final CIRB approval. Any changes/modifications requested by the NCI CIRB at the time of its initial review may require an amendment to the study after distribution if CTEP believes any of the requested changes/modifications should be in the master protocol document (either in the informed consent or in other sections of the protocol document). Minor changes in the informed consent document may be limited to the approved CIRB version of the informed consent document for its sites only. After the trial is activated, all protocol amendments submitted for the trial require NCI CIRB approval prior to final approval of the amendment by CTEP.

Any change to the protocol document subsequent to its approval by CTEP must be submitted to CTEP's PIO in writing for review and approval by CTEP prior to implementation of the change, with the exception of administrative updates. Additional information on the procedures for protocol amendment can be found in the Investigator's Handbook.

1.IV.3.D. Study/Trial Closure

CTEP may request that a phase 1 or phase 2 study be closed to accrual for reasons including the following: (1) insufficient accrual rate; (2) poor protocol performance; (3) protection of patient safety; (4) study results are already conclusive; (5) emergence of new information that diminishes the scientific importance of the study question; and (6) unavailability of study agent. NCI will not provide investigational agents or permit expenditures of NCI funds for a phase 1 or phase 2 study after requesting closure (except for patients on treatment and follow-up).

1.IV.3.E. Data and Safety Monitoring Boards (Data Monitoring Committees)

The NCI ET-CTN Director or designee, assisted by the Biometric Research Branch (BRB) staff, will assess compliance with NCI established policies on Data and Safety Monitoring Boards (DSMBs), also known as DMCs, for ET-CTN LPOs conducting randomized phase 2 studies. These policies must address both the membership of the DSMB/DMC and its operational policies.

The membership of the DSMB/DMC and its policy must be approved by the NCI ET-CTN Program Director. The NCIET-CTN Program Director or designee, assisted by the BRB staff, must review and approve each LPOs policy regarding its data and safety monitoring plans for all ET-CTN studies.

Information on NIH DSMB policies is provided by the *following URLs:*

http://grants.nih.gov/grants/guide/notice-files/not98-084.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines

1.IV.3.F. Data Management &Analysis Review & Use of Standard ET-CTN Tools and Services

At the request of CTEP, the Biometric Research Branch (BRB) staff, in consultation with other NCI/DCTD staff, will review mechanisms established by the Network Site for data management and analysis. When deemed appropriate, BRB staff will make recommendations to ensure that data collection and management procedures are adequate for QC and analysis, yet sufficiently simple to encourage maximum participation of physicians entering patients onto studies and to avoid unnecessary expense. The NCI will have access to all Network Site data although the data will remain the property of the awardee institution under the Cooperative Agreement. Data must also be available for external monitoring as required by NCI's agreement with the FDA relative to the NCI's responsibility as agent sponsor.

During the approval process for study protocols and amendments, NCI/DCTD ensures that these standard ET-CTN tools and services are used. Network Site trial protocols will be periodically audited by NCI/DCTD to ensure that the tools related to common data elements in compliance with the ET-CTN approved sections of the data dictionary for common data elements in caDSR are used in the data collection instruments for the ET-CTN trials. If issues with compliance are identified, the NCI/DCTD will work with the ET-CTN Site to develop a corrective action plan.

1.IV.3.G. Investigational Agent Development and Regulations

The clinical development of new anticancer agents is a highly important use of ET-CTN Site resources. The ET-CTN Sites are a vital component of the research apparatus necessary for the clinical development of the many new investigational agents sponsored by NCI/DCTD. Various branches within DCTD share the responsibilities for investigational agent development, as described below.

1. Biometric Research Branch (BRB): BRB assesses proposed study designs for evaluating the benefits of investigational agents.
2. Cancer Diagnosis Program (CDP): CDP, with other offices in DCTD, may be involved in planning and oversight of clinical trials that require an investigational device exemption (IDE).
3. Cancer Trials Support Unit (CTSU): CTSU coordinates roster management, collection of study specific regulatory documentation, patient enrollment and other ET-CTN support activities.
4. Central Institutional Review Board (CIRB): CIRB coordinates initial, annual, and amendment reviews of protections for human research participants.
5. Clinical Data Management System (CDMS): CDMS supports data management activities. The NCI standard CDMS for the ET-CTN is Medidata Rave®.
6. The Clinical Investigations Branch (CIB): CIB is involved in promoting agents that are first developed into disease-based Phase II and III clinical trials.
7. Clinical Trials Branch in the Cancer Imaging Program (CIP): CIP is responsible for: (1) planning, within CIP as well as with members of the extramural community, overall strategies for studies of new imaging agents in specific tumor types; and (2) coordinating and monitoring trials of new/novel imaging agents under evaluation by the ET-CTN.
8. Clinical Trials Monitoring Branch (CTMB): CTMB verifies adherence by the ET-CTN to the Quality Assurance (QA) procedures of investigational agent trials.
9. Clinical Trials Monitoring Service (CTMS): CTMS coordinates data management, quality assurance and onsite auditing

10. Investigational Drug Branch (IDB): IDB is responsible for: (1) planning, within CTEP as well as with members of the extramural community, overall strategies for studies of new agents in specific tumor types; and (2) coordinating and monitoring trials of new agents developed by the DCTD.
11. Oncology Patient Enrollment Network (OPEN): OPEN provides controls for patient registration, determination of site and investigator eligibility to participate in a particular study, and assessment of patient eligibility according to parameters established in the protocol.
12. Pharmaceutical Management Branch (PMB) at DCTD: PMB provides for the distribution of investigational new agents for which DCTD is the IND sponsor and registration of all investigators and associates participating in CTEP clinical trials and the maintenance of all registration records.
13. Regulatory Affairs Branch (RAB): RAB maintains close contact and ongoing dialogue with the pharmaceutical collaborator and with the FDA to ensure that new agent development complies with federal regulations and proceeds in a coordinated way.
14. Regulatory Support Service (RSS): RSS provides roster management and collection of study specific regulatory documentation.

As previously stated, NCI/DCTD (including CTEP and CIP) uses a system of Letters of Intent (LOIs) and PTAs as a mechanism for developing rational strategies for investigational drug/agent development studies as described in the Investigator's Handbook which includes a full description of the process for the clinical development of investigational agents and summary of the responsibilities of investigators conducting these trials.

1.IV.3.H. Compliance with Federal Regulatory Requirements Review

CTMB and RAB staff will review general policies and procedures periodically, as needed, and provide advice regarding mechanisms established by the Networks to meet FDA regulatory requirements for studies involving DCTD/CTEP-sponsored investigational agents and OHRP requirements for the protection of human subjects.

1.IV.2.G. Changes in Principal Investigator(s) for Any Key Component of the ET-CTN

The ET-CTN Director must approve any proposed changes in the PI for any key component for the ET-CTN under the Cooperative Agreement. The institution's business office should forward the name of the proposed PI in a memorandum to the ET-CTN Director requesting approval, with a copy to the NCI/DCTD Senior Program Specialist. The curriculum vitae (CV) of the proposed PI should be included as an attachment. The memorandum should be countersigned by the current PI (if available), the business official who has responsibility to sign for the grant, and the proposed PI.

1.IV.2.H. Changes in Awardee Institution for Any Key Component of the ET-CTN

Only under exceptional circumstances will NCI permit transfer of a Cooperative Agreement from one institution to another. The ET-CTN Director, NCI/DCTD Senior Program Specialist, and the appropriate NCI Grant Specialist should be consulted for further advice if the LAO contemplates such a transfer request. Any such request, if accepted, will require a detailed plan regarding policies and procedures related to personnel issues, resources, etc., and approval and oversight by the ET-CTN Director and Associate Director, CTEP.

NIH prior approval is required for the transfer of the legal and administrative responsibility for a grant-supported project or activity from one legal entity to another before the expiration of the approved project period (competitive segment). A request for a change of grantee organization must be submitted

to the NCI Office of Grants Administration (OGA). The original institution must include an Official Statement Relinquishing Interests and Rights in a Public Health Service Research Grant (PHS 3734) (relinquishing statement). The relinquishing statement may be submitted in paper or electronically via the eRA Commons. Final FFR Expenditure Data and a Final Invention Statement are due to NIH from the relinquishing organization no later than 90 days after the end of NIH support of the project. Final FFR Expenditure Data should not be submitted until the original institution has received a revised NoA for the relinquished grant.

The proposed new grantee institution must provide the OGA with a change of institution application which may be submitted using the PHS 398 or PHS 416-1 paper application forms, or electronically via Grants.gov using the Parent Funding Opportunity Announcement listed at: http://grants.nih.gov/grants/guide/parent_announcements.htm.

The paper application from the proposed new grantee institution should include, at a minimum, the following:

1. PHS 398 Face page
2. Budget pages (current and future years). (Under awards resulting from modular applications, the application should include narrative budget information for the current budget period, including total direct cost and the basis for computing F&A costs and, if applicable, future budget periods.) Budgets should not exceed the direct costs (plus applicable F&A costs) previously recommended for any budget period. For transfers in the middle of a budget period, the budget for the initial year may be based on the total costs relinquished only if the grantee has been instructed to do so by the awarding IC. For these applications, grantees will also need to include the Other Project Information and the Senior/Key Personnel components.
3. Updated biographical sketches for the PD/PI and existing senior/key personnel and biographical sketches for any proposed new senior/key personnel.
4. If transferring on the anniversary date, include the progress report for the current year including a statement regarding the goals for the upcoming year. For all transfer applications include also a statement indicating whether the overall research plans/aims have changed from the original submission, and, if so, provide updated information.
5. Updated "other support" page(s), if necessary.
6. Resources page, including probable effect of the move on the project.
7. Checklist page
8. Certification of IRB/IACUC approval, including OHRP and OLAW assurance numbers, if applicable.
9. Detailed list of any equipment purchased with grant funds to be transferred to the new organization (inclusion of this list in the transfer application from the new organization indicates its acceptance of title to that equipment).

For more information see: http://grants.nih.gov/grants/policy/nihgps_2012/nihgps_ch8.htm.

1.V. Other NCI Administrative Considerations

1.V.1. Program Staff Administration of the ET-CTN

Within NCI/DCTD, major scientific policy and programmatic decisions concerning the ET-CTN are made only after appropriate consultation with and involvement by the responsible ET-CTN Director, the Co-

Program Directors of the ET-CTN, the Project Scientists, NCI/DCTD Branch Chiefs and Program Chiefs that are involved in the ET-CTN, and the Associate Director, CTEP, DCTD, as necessary and appropriate. Routine programmatic administration is the responsibility of the ET-CTN Director, who assures uniformity of implementation across the various key components in conjunction with the Co-Program Directors of the ET-CTN and the Project Scientists.

The ET-CTN Director or his/her designee has responsibility for addressing and approving non-competitive award (Type 5) budget requests, any supplemental budget requests, and new/competitive award (Type 1) budgets, as well as future Type 2 applications. The responsible ET-CTN Director will administer these tasks in conjunction with the Grants Specialist in the Office of Grants Administration (OGA) and will be assisted by the Co-Program Directors of the ET-CTN, the Project Scientists for the key components of the ET-CTN, as well as the NCI/DCTD Senior Program Specialist for the ET-CTN.

1.V.2. Senior Program Specialist for the ET-CTN

The NCI/DCTD Senior Program Specialist (Mrs. Kim Witherspoon) for the ET-CTN works closely with the ET-CTN Director in reviewing administrative materials supporting ET-CTN Sites requests, performing budget analyses, and facilitating the completion of action items involving coordination between NCI/DCTD, the NCI Office of Grants Administration (OGA), and the ET-CTN awardees. The NCI/DCTD Senior Program Specialist exchanges information with the sites for the key components of the ET-CTN and OGA staff on administrative changes and priorities.

1.V.3. NCI Office of Grants Administration (OGA)

The Grants Specialist for the NCI Office of Grants Administration (OGA) is responsible for the fiscal and administrative aspects of each application and award. The Grants Specialist for OGA works closely with the responsible NCI ET-CTN Director and NCI/DCTD Senior Program Specialist to assure that appropriate science is funded in accordance with applicable laws, regulations, policies, and peer review recommendations to the extent that the budget allows and NCI priorities dictate.

1.V.4. Miscellaneous Budgetary Considerations

1.V.4.A. Carryover Requests

Carry-over requests will be entertained in situations where circumstances prevented funding from being spent during the budget period for which it was provided and where funding is not replicated in the current budget year for an ongoing expense.

1.V.4.B. Requests for Non-competing Supplemental Funding

Informal discussions about the possibility of receiving non-competing supplemental funding for special needs and/or additional funding to cover data collection and management, and biospecimen collection may be initiated by the LAO PI. However, formal requests must be made for funding to be received and must always be countersigned by the institute business official responsible for the Cooperative Agreement/grant and the PI(s). Electronic facsimile signatures on documents transmitted via email are acceptable. Most requests, however, will require the use of a Form PHS 398/SF424or PHS 2590 to capture the details of the requested budget. The original should be sent to the ET-CTN Director, in care of the NCI/DCTD Senior Program Specialist.

Part 2: Guidelines for Submission of Competing New Applications & Description of Review Process

2.I. Pre-Application Consultation and Application Submission Instructions

2.I.1. General Considerations and Due Dates

All competing new applications (Type 1) for support through the NCI Early Therapeutics Clinical Trials Network (ET-CTN) must be submitted under the appropriate Funding Opportunity Announcement (FOA). The FOA (RFA-CA-13-006) contains essential information on various aspects of the components including the eligibility requirements for the applicant institution/organization and PI(s).

All new applications must be prepared using the most currently revised PHS 398 research grant application instructions and forms – or SF424 (Research & Related [R&R]) application once the electronic application replaces the PHS 398 for the Cooperative Agreements. The major components of the PHS 398, as described in these Guidelines for the ET-CTN, are retained in the SF424. Hence, applicants should follow the same instructions provided in these Guidelines regardless of whether they are using the PHS 398 or SF424 application. The PHS 398 is available at: http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact: **GrantsInfo,** Telephone (301) 435-0714, **Email:** **GrantsInfo@nih.gov**. Once the SF424 is required for applications submitted for the ET-CTN, applicants will be notified by NCI/DCTD Program staff. Applicants should use the appropriate NIH website references available at: http://grants.nih.gov/grants/funding/424/index.htm to access information regarding submission of the SF424.

It should be noted, however, that the standard instructions included in the PHS 398 and SF424 applications are designed primarily for individual research projects, and do not address the unique goals and policies of the ET-CTN. **These Guidelines are only meant to supplement the PHS 398/SF424 instructions, except where it is explicitly noted that these Guidelines are replacing or supplanting instructions in the PHS 398/SF424 application (e.g., the format for the research plan is different for these applications). If an issue is not explicitly included in these Guidelines, then applicants should follow** the information and guidance given in the PHS 398/SF424.

> Applications not prepared using the current version of the PHS 398 application forms (or SF424 electronic application when it replaces the PHS 398) or not adhering to the format and preparation instructions contained in these Guidelines and the ET-CTN Funding Opportunities Announcement (FOA) may be returned without review or not reviewed. Organizations submitting new applications under the ET-CTN FOA MUST apply for five (5) years of support. Applications requesting less or more than 5 years of support may be returned without review.

The receipt dates & review schedule for all new competing applicationsfor5 years of support should be submitted in response to the FOA for the ET-CTN as summarized below:

Application Submission & Review Activity	Due Date
Pre-consultation with NCI/DCTD	4 to 6 months prior to Application Due Date
Letter of Intent Due Date	March 23, 2013
Application Due Date	August 23, 2013
Post Submission Application Materials	30 Days Prior to Scientific Merit Review Meeting
Scientific Merit Review	October – November 2013
Advisory Council Review (NCAB)	January 2014
Earliest Start Date	February 2014
Just-in-Time Information	Prior to Start Date

2.I.2. Initial Communications and Letter of Intent

Initial Communications with NCI/DCTD Staff – 4 to 6 Months Before Application Due Date: Although it is not required, it is strongly recommended that prospective applicants schedule a pre-application consultation with NCI/DCTD Program Staff including the ET-CTN Director (Dr. S. Percy Ivy) and appropriate Scientific Program/Project Officers approximately four (4) to six (6) months in advance of the application due date. This consultation is intended to help the PI (along with multiple PIs and/or co-investigators) to clarify the ET-CTN application and discuss all relevant aspects of the application process. NCI/DCTD staff will clarify the intent of the Guidelines and current NCI budget allocations, and describe the peer-review process. To schedule the pre-application consultation, prospective applicants should send a request to the NCI/DCTD ET-CTN Program Director electronically:

Prior to March 21, 2013:
Dr. S. Percy Ivy
Associate Branch Chief
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
6130 Executive Boulevard, EPN Room 7131, MSC 7246
Bethesda, MD 20892 (for U.S. Postal Service express or regular mail)
Rockville, MD 20852 (for express/courier delivery; non-USPS mail)
Email: ivyp@ctep.nci.nih.gov

After March 21, 2013:
Dr. S. Percy Ivy
Associate Branch Chief
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
9609 Medical Center Drive, Room 5-W-458

Rockville, MD 20850
Email: ivyp@ctep.nci.nih.gov

Letter of Intent – Deadline: March 23, 2013
Prospective applicants are asked to submit a LOI that includes the following information:

1. Descriptive title of proposed research.
2. Name(s), address(es), telephone number(s), and email address of the PI(s).
3. Names and email addresses of other key personnel.
4. Participating institutions.
5. Number and title of this funding opportunity.

Although an LOI is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NCI staff to estimate the potential review workload and plan the review. In addition, if informational sessions are planned, it will allow NCI staff to contact interested applicants directly.

The LOI is to be sent by March 23, 2013. The earliest anticipated start date is in February 2014.

The LOI should be sent to:

Prior to March 21, 2013
Dr. S. Percy Ivy
Associate Branch Chief
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
6130 Executive Boulevard, EPN Room 7131, MSC 7246
Bethesda, MD 20892 (for U.S. Postal Service express or regular mail)
Rockville, MD 20852 (for express/courier delivery; non-USPS mail)
Telephone: (301) 496-1196
Fax: (301) 402-0428
Email: ivyp@ctep.nci.nih.gov

After March 21, 2013
Dr. S. Percy Ivy
Associate Branch Chief
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
9609 Medical Center Drive, Room 5-W-458
Rockville, MD 20850
Telephone: (301)
Email: ivyp@ctep.nci.nih.gov

2.I.3. Application Submission Procedures

Applications must be prepared using the PHS 398 research grant application forms and instructions (unless they have converted to electronic submission) for preparing a research grant application. Submit a signed, typewritten original of the application, including the checklist, and three (3) signed photocopies in one package to the Center for Scientific Review at the address listed below. **The original must be signed by the Project Director/Principal Investigator (PD(s)/PI(s)) and an authorized organizational or institutional official.**

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

Personal deliveries of applications are no longer permitted (see: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-040.html).

At the time of submission, two (2) identical, single-sided paper copies of the original application and one (1) CD containing appendix material (if permitted) must be sent to the address listed below. Please Note: Applicants may include additionally a CD with a bookmarked pdf file of the application. All appendix material (if allowed for the ET-CTN key component) must be prepared as bookmarked PDF files on a CD following the PHS 398Guidelines.

Referral Officer
Division of Extramural Activities
National Cancer Institute
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892-8329 (for U.S. Postal Service regular or express mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-3428
FAX: (301) 402-0275
Email: ncirefof@dea.nci.nih.gov

Applications must be **received on or before the application receipt date(s)** described above (Section IV.3.A.). If an application is received after that date, it will be returned to the applicant without review.

Upon receipt, applications will be evaluated for completeness by the Center for Scientific Review (CSR) and for responsiveness by the NCI. Incomplete and/or non-responsive applications will not be reviewed. The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW application. That is, the application for the funding opportunity must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Information on the status of an application should be checked by the PI in the eRA Commons at: https://commons.era.nih.gov/commons/.

2.I.4. Appendix Material

Per the NIH/NCI policy on what may be submitted as appendix materials (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-077.html), **the information provided below specifies if appendix materials are allowed as part of the application for the key components of the ET-CTN, as well as the type of appendix material that may be included.** All appendix materials for paper applications submitted on the PHS 398 form must be submitted as book marked PDF files on CDs. A summary listing of all the items included in the appendix is encouraged but not required. When including a summary, it should be the first file on the CD.

Follow the standard instructions for preparing the CDs:

1. Use PDF format only. The files should be prepared as PDF version no higher than 1.4 for compatibility with NIH programs and software.
2. Where possible, applicants should avoid creating PDF files from scanned documents. NIH recommends producing the documents electronically using text or word-processing software and then converting the document to PDF format. Scanned document images should be checked for legibility.
3. Label each disk with the date, PI's Name, Grant Number (if available), grant title, and applicant institution.
4. If burning CD-ROM disks on a Mac, select the ISO 9660 format.
5. Do not use compression techniques for the electronic files.
6. Do not use password protection, encryption, digital signature and/or digital certification in the PDF files.

Applications for the ET-CTN are scanned by central NIH offices to produce black and white images and black and white double sided copies for the reviewers. Figures in the application that do not reproduce well in black and white may be included in the application and allowed Appendix material. However, all figures included in the appendix material must be included in the application, although they may be reduced in size in the application. Images not included in the application cannot be included in the appendix.

If your application contains a large number of color illustrations or charts and graphs that will not reproduce well in black and white, you may also submit a CD with a bookmarked PDF file of the entire application along with the two copies of the application sent to the NCI Referral Office on the due date. Such CDs will be accepted only at the time of application submission.

Appendix materials must be included with the copies of the application sent to the NCI Referral Office on the due date as specified above in Part 2 – Section 2.I.1 of these Guidelines. Appendix material cannot be used to circumvent page limitations of the research plan. Follow all instructions for the Appendix (please note all format requirements) as described in the PHS 398 Application Guide.

Applicants can provide the following information (and only the following information) in the appendix material for their respective applications as described below.

Applicants may submit up to 3 of the following types of publications:

1. Manuscripts and/or abstracts accepted for publication but not yet published that are referenced in the Research Plan of the application.
2. Published manuscripts and/or abstracts that are referenced in the Research Plan of the application **only** when a free, online, publicly available journal link is not available.
3. Patent materials directly relevant to the application.

Other Information:

1. Paper PHS 398 applications **only** may include full-sized glossy photographs of material such as electron micrographs or gels in the Appendix; however, an image of each (may be reduced in size but readily legible) must also be included within the page limitations of the Research Plan.
2. The following items are encouraged for inclusion in the Appendix: two sample institutional early phase experimental therapeutic protocols activated during the preceding award period or in the last 3 years, including templates, if appropriate; standard operating procedures (other than study and data monitoring and conflict of interest policies), and protocol and informed consent document templates.

2.I.5. Notification of International Involvement in ET-CTN Trials

The ET-CTN Lead Academic Organization (LAO) should alert the NCI/DCTD Senior Program Specialist (Mrs. Kim Witherspoon) when the new competing application involves any international (non-US) component. In such cases, advance clearance from the U.S. Department of State is required for each non-US component prior to the award. The information required by U.S. Department of State is listed below (this information should also include all non-US subcontracts).

1. Estimated annual Total Cost dollar award for the non-US component.
2. Name, organization, city, and country of the International (non-US) Principal or Collaborating Investigator(s).
3. Biosketch and Curriculum Vitae (CV) for both the domestic PI and the international PI.
4. OHRP assurance number (i.e., Federalwide Assurance number) for the non-US component.
5. Brief summary of responsibilities and work to be performed for the non-US component.

Only U.S. and Canadian institutions are eligible to apply. Other Foreign institutions may participate in the program through collaborations with either U.S. or Canadian applicant organizations.

Several special provisions apply to applications submitted by foreign organizations:

1. Charge back of customs and import fees is not allowed.
2. Format: every effort should be made to comply with the format specifications, which are based upon a standard U.S. paper size of 8.5" x 11."
3. Funds for up to 8% administrative costs (excluding equipment) can now be requested (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-028.html).
4. Organizations must comply with Federal/NIH policies on human subjects, animals, and biohazards.
5. Organizations must comply with Federal/NIH biosafety and biosecurity regulations. See Section VI.2. Administrative Requirements, "Cooperative Agreement Terms and Conditions of Award."
6. Additional information regarding Foreign grants is available in the NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/nihgps_2012/nihgps_ch16.htm#_Toc271265275).
7. Applications from Foreign (non-U.S.) institutions submitted using the **PHS 398**: Follow the NON-MODULAR FORMAT instructions and submit Form Page 4 and Form Page 5. Do not complete or submit the Modular Budget Format Page.

Proposed research should provide special opportunities for furthering research programs through the use of unusual talent, resources, populations, and/or environmental conditions in other countries that are not readily available in the U.S. or that augment existing U.S. resources.

2.II. New Applications Format and Budget Considerations

2.II.1. General Information and Common Budget Outline for the ET-CTN

All applications for key components of the ET-CTN must follow the PHS 398/SF424 format for new applications, including formatting and page limitations except as modified below. The applications should describe the scientific and administrative experience of key personnel and should include and follow the PHS 398/SF424 instructions for Biographical Sketches and Other Support information (including support for clinical trials activities). In the section entitled “Key Personnel” in the PHS 398/SF424, it is imperative that applicants list all individuals participating in the scientific execution of the main activities of the ET-CTN in the format specified (i.e., name, organization [their institutional affiliation], and role on the project), including those with no requested salary support. Under “Role on the Project”, indicate how the individual will function with regard to the ET-CTN.

A roster of Key Personnel should be included with each application. Key Personnel will usually include the PI (and multiple PIs, if applicable), other significant scientific, technical and administrative officers as well as major committee chairs and vice-chairs. Consultants should be included if they meet the definition of “Key Personnel." Applicants must ensure the list of Key Personnel is complete, and may use as many continuation pages as necessary. Although information on "Other support" is required for all Key Personnel listed on all applications that are to receive grant awards, information on “Other Support” should NOT be submitted with the application. Rather, NIH will request complete and up to date "Other Support" information from applicants at an appropriate time following peer review. The NIH’s scientific program and grants management staff will review this information prior to award (see “Just-in-Time” information in this section of the Guidelines).

> **Please Note:** All pages must be numbered sequentially within a submitted application. All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the internet sites. Furthermore, reviewers are cautioned that their anonymity may be compromised when they directly access an internet site. **The exception to this is the URL for published manuscripts and abstracts via PubMed as only the public internet references for these publications are accepted in the application.**

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at: http://grants.nih.gov/grants/policy/nihgps_2012/index.htm.

Pre-award costs are allowable. A grantee may, at its own risk and without NIH prior approval, incur obligations and expenditures to cover costs up to 90 days before the beginning date of the initial budget period of a new or competing continuation award if such costs are necessary to conduct the project, and would be allowable under the grant, if awarded, without NIH prior approval. If specific expenditures would otherwise require prior approval, the grantee must obtain NIH approval before incurring the cost.

NIH prior approval is required for any costs to be incurred more than 90 days before the beginning date of the initial budget period of a new or competing continuation award.

The incurrence of pre-award costs in anticipation of a competing or non-competing award imposes no obligation on NIH either to make the award or to increase the amount of the approved budget if an award is made for less than the amount anticipated and is inadequate to cover the pre-award costs incurred. NIH expects the grantee to be fully aware that pre-award costs result in borrowing against future support and that such borrowing must not impair the grantee's ability to accomplish the project objectives in the approved time frame or in any way adversely affect the conduct of the project. See the NIH Grants Policy Statement at: http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part6.htm.

This FOA uses non-modular budget formats described in the PHS 398 application instructions (see: http://grants.nih.gov/grants/funding/phs398/phs398.html).

Follow the current PHS 398 instructions to provide a detailed budget (direct costs) for the entire application for the first 12-month period (Form page 4) and the entire proposed project period (Form page 5). Use additional Form Pages 4 and 5 to provide detailed separate budget information (first year and cumulative budgets for the entire project period) for the following application components:

1. Scientific Leadership & Site Organization
2. Team Science for Project Development
3. PK/PD, Biomarker Assays, and Molecular Characterization of Patients
4. Coordination of Clinical Trials and Associated Activities
5. Research Pharmacy Management
6. Career Development and Mentored Training of Junior Investigators

Important Note on Budget: The requested budgets should take into consideration the standardized central operational, regulatory and administrative support provided by NCI. These services will be directly funded by the NCI and respective cost must not be included in the requested budgets.

The budget should include (in addition to support for scientific leadership, administrative and regulatory activities, data management and analysis, and travel, etc.) the following items:

1. Scientific Leadership and Site Organization Funds for travel. The LAO PD(s)/PI(s) will be required to travel to four IDSC meetings per year. Travel funds for two NCI/CTEP Early Drug Development (EDD) meetings per year for three representatives from the ET-CTN Site (at least one of whom must be the LAO PD/PI and for two presenters for major national/international meetings should be included in the budget for Scientific Leadership).

2. PK/PD, Biomarker Assays, and Molecular Characterization Research Funds for laboratory studies (e.g., PK and PD studies) performed on specimens (e.g., blood, tumor tissue, buccal cells, etc.) obtained from participants enrolled on ET-CTN clinical trials. Include this within the PK/PD, Biomarker Assays, and Molecular Characterization of Patients budget pages. Note: Biomarker assays will be prioritized and funded separately through administrative supplements. Other biomarker assays will require other sources of funding.

   Pharmacology and specimen acquisition to be allocated to support institutional costs of research that are not considered “a cost of treatment” by medical insurers, and therefore are not reimbursed by insurers (e.g., blood and urine collection and shipping for PK studies, tumor

tissue handling and shipping to the tissue bank or pathology component, and performance of research imaging studies).

3. Coordination of Clinical Trials and Associated Activities Research Funds to be allocated to support institutional costs of research that are not considered "a cost of treatment" by medical insurers and, therefore, are not reimbursed by insurers (e.g., blood and urine collection and shipping for PK studies, tumor tissue handling and shipping to the tissue bank, and performance of research imaging studies). Include this cost within the Coordination of Clinical Trials and Associate Activities budget pages.

   The budget for early clinical trials of new anticancer agents with early-phase emphasis should include funding to be allocated to support research and development and ET-CTN collaboration (in addition to support for scientific leadership, administrative and regulatory activities, data management and analysis, etc.).

   All costs for onsite data management using Medidata Rave and services provided by CTMS must be fully justified. The cost of mailing or handling research-related patient specimens, forms, and materials should be included. Other consulting costs should be outlined.

   Coordination of Clinical Trials and Associated Activities (protocol development, and statistics and data management) for the institution(s) costs to support the non-accrual responsibilities associated with participating in early-phase experimental therapeutic clinical trials (e.g., CIRB submission, amendment distribution and continuing review, site training, pharmacy set-up, and site administration) that must be met even if patients are never enrolled on a study at an institution. An annual accrual rate of at least 50 patients per year should be assumed.

4. Career Development and Mentored Training of Junior Investigators Funds (approximately 3% of the total budget request) for activities to develop junior investigators/junior faculty through mentorship and other initiatives. Junior investigator career development and mentored training costs should be addressed in the research plan in the proposed budget.

2.II.2. Research Plan

All instructions in the PHS 398 Application Guide must be followed, with the following additional instructions.

Research Strategy: The Research Strategy should consist of the following sub-sections:

1. Overview of Relevant Capabilities and Past Performance – 6 pages
2. Scientific Leadership & Site Organization – 12 pages
3. Team Science for Project Development – 6 pages
4. PK/PD, Biomarker Assays, and Molecular Characterization of Patients – 6 pages
5. Coordination of Clinical Trials and Associated Activities – 12 pages
6. Research Pharmacy Management – 6 pages
7. Career Development and mentored Training of Junior Investigators – 6 pages

The number of pages for the Research Strategy has been specified above. The applicant is encouraged to use the minimum number of pages necessary to clearly and succinctly describe the research plan. The pages (or fewer) should be apportioned as desired by the applicant to cover these sections.

SOPs and policies of the ET-CTN related to study monitoring, Data Monitoring Policy, and Conflict of Interest Policy should be included in Section E, Protection of Human Subjects, in the application. All others should be included in the appendix.

2.II.2.A. Sub-section A: Overview of Relevant Capabilities and Past Performance − 6 pages

In this sub-section, applicants should summarize their ability and experience to conduct clinical trials and experimental therapeutic agent development. Describe relevant clinical and research activities related to the development of investigational agents either held under IND in collaboration with the NCI or performed as part of other academic pursuits.

1. **Applicants representing current awardees of the Early Phase Clinical Trials Program:** Cover in this narrative your role and accomplishments under the current award.

2. **Applicants previously unaffiliated with the Early Phase Clinical Trials Program:** Describe experiences, accomplishments, infrastructure, capabilities, etc., relevant to the ET-CTN objectives defined in this FOA.

Specific information to provide must include (but is not limited to) the following aspects:

A. Skills and accomplishments of all PDs/PIs in overseeing clinical trials of experimental cancer therapeutics.
B. Funded peer-reviewed grants that led to clinical trials or resulted in a clinical trial from hypothesis-driven research funding.
C. Highlights of published results from clinical and basic research fostered by or associated with peer-reviewed grant funding.
D. The ability of the investigators (documented by past performance) to collect a sufficiently high percentage of specimen samples on clinical trials with correlative science endpoints.
E. Summarize accomplishments of the participants in the proposed ET-CTN site with regard to Letters of Intent (LOIs) for clinical trials submitted, LOIs approved, actual patient accrual, and annual accrual.

2.II.2.B. Sub-section B: Scientific Leadership & Site Organization – 12 pages

In this Sub-section, describe the qualifications and experience of the scientific leadership, their plans for participating in ET-CTN activities, and the organization of the proposed ET-CTN site. Specifically, applicants are required to address, at a minimum, the following aspects:

Scientific Leadership

Provide a brief overview of the qualifications and experience in oncology drug development research of PD(s)/PI(s) and other key personnel at the ET-CTN site. Note that PD(s)/PI(s) are expected to be national and international leaders in the relevant areas of science and have documented administrative leadership experience.

Outline how the PD(s)/PI(s) intend to accomplish productive collaborations between participating ET-CTN sites and other clinical and translational research investigators from their institution or from other institutions internal and external to the ET-CTN using a team science approach. Include plans to ensure effective interaction, communication, and monitoring performance within the ET-CTN sites to facilitate clinical trial protocol development, safety, and timely protocol conduct. These procedures should address:

1. Accrual of adequate number of eligible patients to ET-CTN trials.
2. Timely submission of required data to Medidata Rave.
3. Observance of clinical trial protocol requirements.
4. Contributions to clinical trial protocol development and conduct.
5. Authorship in ET-CTN-related publications.
6. Participation in ET-CTN administrative and scientific committees.
7. Rapid publication of clinical trial and laboratory study results and actions to be taken when time lines for the development of abstracts and manuscripts are not met.

Outline plans for the Leadership to assure timely preparation, presentation, and publication of clinical trial results and research findings at international meetings and scientific journals.

Describe available biostatistical expertise that will be increasingly needed for ET-CTN studies, including the capabilities of the team in analyses that combine clinical endpoints with sophisticated molecular data. (Biostatisticians with expertise and experience with these types of analyses are required as a part of the leadership team.)

List the physician(s) responsible for patient management if the LAO PD/PI is not a practicing physician.

ET-CTN Site Organization

Outline the organization of the proposed ET-CTN site, including the awardee institution (i.e., LAO), any LAO Integrated Components, and any participating AOs. Address all items listed below. In addition to the narrative, provide appropriate organizational charts.

1. The Leadership structure planned to oversee all clinical trials operations.
2. Plans to oversee the conduct of early phase therapeutic clinical trials. Sites are expected to have the requisite statistical expertise for trial design/monitoring and coordinating patient enrollment on all clinical trials open in the ET-CTN.
3. Establish an internal committee to oversee and monitor patient safety, protocol compliance, and outcome and response review.
4. Describe the organizational structure and documented procedures for coordinating protocol development, including timelines and actions taken when these timelines are not met. These timelines should include LOI and protocol development, study activation, and completion, activation and submission of abstracts and manuscripts.
5. Describe LAO and AO (if applicable) research capabilities, including but not limited to:
    A. Abilities of the LPO to develop, write, implement, and monitor ET-CTN protocols at the AO site, and at other ET-CTN LAOs.
    B. Clinical and/or basic research experience, training, time availability, research competence, and commitment to early phase experimental therapeutics program participation of the institutional PD/PI, as evidenced by past clinical research contributions and current research efforts relating to oncology early drug development.
    C. Documented ability to meet the intensive data collection and regulatory requirements necessary for early phase experimental therapeutic clinical trials. Institutional data management resources and plans for utilizing these resources for timely data submission for early phase experimental therapeutic clinical trials should be described.
    D. Documented ability of the LAO to accrue at least 50 patients per year and documented ability of each AO (if applicable) to accrue approximately 25 patients per year to early

phase experimental therapeutic clinical trials. Provide documentation and examples of past successful cooperative interactions.

E. Availability of state-of-the-art imaging and the institutional commitment for utilizing these methodologies in the conduct of early phase experimental therapeutics studies when such imaging studies are required.
F. Clinical and laboratory areas of scientific expertise resident at the LAO and AO(s) that are applicable to oncology drug development and that the institutions are willing to utilize these areas for the conduct of early phase experimental therapeutics assays and correlative studies (e.g., PK, pharmacogenomic, and PD monitoring or imaging research studies, laboratories that meet Clinical Laboratory Improvement Amendments [CLIA] standards.

6. Outline plans for an internal ET-CTN site committee, including its anticipated composition. It is expected that such an internal committee will generally facilitate interactions of member site investigators. The internal ET-CTN site committee should be able to review progress and treatment-related toxicities, establish priorities, and plan future clinical trial research activities.
7. For multi-institution applications, provide evidence of well-established collaborations, clearly described procedures, and a strong justification for multi-institution participation. Include a description of the criteria used to select AOs. Multiple institution applications should provide evidence of a detailed governance plan indicating how scientific and fiscal decisions are made.

Outline institution commitment to facilitate participation in ET-CTN clinical trials for patients desiring participation.

2.II.2.C. Sub-section C: Team Science for Project Development – 6 pages

ET-CTN sites will be expected to lead and/or participate in multi-disciplinary scientific teams during the development and implementation of ET-CTN drug development plans. In this section, describe relevant experience of the applicant team in the conduct and management of team science projects. Address plans with regard to such aspects as:

1. Promoting cooperation between investigators across disciplines, and developing preclinical projects that will guide clinical agent development.
2. Enhancing existing capabilities and adapting new approaches to reach collaborative team goals by leveraging expertise within and across institutions.
3. Procedures for addressing failure by investigators and/or institutions to meet study timelines and objectives.
4. Assessing clinical results and defining scientific criteria for subsequent prioritization of agent development.

Provide an example of an inter- and trans-disciplinary team project focused on early drug development (ongoing or previously completed). The example should demonstrate cooperation and coordination among investigators across disciplines in the investigation of a research question in a coherent fashion. The roles for each team member and the methods and/or processes that the team utilizes to promote a team effort in answering complex research challenges should be clearly articulated. These activities should demonstrate enhancements of existing capabilities and new approaches to reach the goals of the collaborative team.

This example may include, but is not limited to, the description of activities such as:

1. Research topic selection
2. Identification and integration of scientific collaborators.
3. Definition of leadership responsibility.
4. Decision-making authority.
5. Project coordination.
6. Communication within the team.
7. Data access.
8. Resource management.
9. Conflict resolution.
10. Guidelines implemented for authorship.
11. Management of intellectual property (IP).
12. Collective management.

The example to be provided is for purposes of peer review only. There is no expectation that the project described will be implemented or funded within the ET-CTN. It will serve as a representative example of the groups' ability to select and constitute a highly multi-disciplinary team project. Examples that go beyond the LAO to include organizations involved in early phase experimental therapeutics are encouraged.

2.II.2.D. Sub-section D: PK/PD, Biomarker Assays, and Molecular Characterization of Patients – 6 pages

In this section, outline expertise in PK/PD and acquisition/analysis of clinical specimens. Describe unique molecular characterization capabilities available at ET-CTN sites that can be utilized to analyze patients on ET-CTN trials. Address such elements as:

1. Conducting appropriate pharmacology studies in clinical trials.
2. Participating in the molecular characterization of all patients enrolled on early phase therapeutics trials, and demonstrating the requisite expertise in acquiring fresh biopsy specimens from a high percentage of patients on trials, even if invasive procedures are required.
3. Planning and implementing appropriate PD, pharmacogenomic, and imaging studies integrated with clinical trials conducted by the ET-CTN.
4. Developing validated assays – assays used for patient selection, stratification, or determination of treatment must be performed in a CLIA-certified laboratory, and may be subject to FDA oversight as an investigational device exemption (21 CFR 812).
5. Using validated molecular imaging capabilities, as appropriate.
6. Coordinating the acquisition, handling, preparation, evaluation, and shipment of specimens to ET-CTN sites and/or tumor banks/biorepositories.
7. Evaluating translational endpoints in clinical trials of investigational agents (e.g., the levels of expression and/or activity of molecular targets and/or downstream effectors pertinent to a given agent).
8. Analyzing tumors and specimens with genomic and expression arrays or other biomarker-based studies to define response and resistance mechanisms and to identify follow-on therapy and investigational combination treatment regimens.
9. Lab-based assays or biomarkers developed into fit for purpose assays ready to be transferred to or already implemented in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.
10. Describing approaches to development of SOPs for assay validation (molecular).
11. Tissue handling and storage facilities.

12. Proposed imaging methods, and timelines to incorporate imaging endpoints into the overall research program. Include the availability of adequate post-acquisition image storage, processing, and analysis capabilities.

For patient molecular characterization, applicants should describe their expertise in the acquisition and analysis of high quality clinical specimens. Describe also experience, expertise, and procedures for validating and conducting studies using genomics, expression, analysis, or other assay-driven integral biomarker evaluations such as:

1. Genomic analysis of patient specimens with identification and reporting of actionable mutations;
2. Expression array analysis of patient specimens, and reporting and analysis of derived data;
3. Proteomic or phosphoproteomic evaluation of patient specimens during treatment, and reporting and analysis of results; and
4. Assay or biomarker integral or integrated studies on patient specimens, and reporting of results.

2.II.2.E. Sub-section E: Coordination of Clinical Trials and Associated Activities– 12 pages

Applicants should describe their experience and the proposed management of complex early phase clinical trials, including protocol development, patient accrual, data and specimen management, and compliance with regulatory statutes. Clinical trials must be conducted in accordance with the Investigator's Handbook, A Manual for Participants in Clinical Trials of Investigational Agents Sponsored by the Division of Cancer Treatment and Diagnosis, National Cancer Institute (http://ctep.cancer.gov/handbook).

The application should address the items specified below:

Protocol Development and Clinical Trial Execution

1. Procedures developed and utilized to support the timely development, activation, and completion of early phase clinical trials for adults with cancer.
2. Procedures for training and maintaining the proficiency of institutional personnel in the successful management of early phase therapeutic clinical trials.
3. Procedures for coordination and tracking of study modifications/amendments.
4. Procedures for determination of patient eligibility and assigning drug dose level.
5. Statistical support for all aspects of the ET-CTN clinical trials.
6. Personnel needs to support clinical trials performed by the research project team by identifying, recruiting/affiliating, and retaining qualified personnel necessary for the conduct of clinical trials.
7. Timely review and assessment of clinical trial data, and interim evaluation and consideration of measures of outcome, as consistent with patient safety and good clinical practice (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf).
8. Facilitating member interactions and communications for single institution or multi-institution sites.

Data Management

1. Procedures for on-site data management, including interactions with on-site and CTMS data management personnel, data transmittal via Medidata Rave to CTMS, data editing, timely resolution of queries from CTMS, quality control, and verification of submitted data.

2. Procedures for complying with onsite auditing, including the use of Medidata Rave and a description of how auditing will be coordinated.
3. Plans to establish and maintain site, investigator and associate rosters with the Cancer Trials Support Unit (CTSU).

Regulatory Compliance

1. Provide a general description of the data and safety-monitoring plan as part of the research application. This policy should be consistent with NIH and NCI guidelines for data monitoring in early phase experimental therapeutic clinical trials.
2. Procedures for expedited reporting of all serious and/or unexpected adverse events via Adverse Event Expedited Reporting System/Cancer Adverse Event Reporting System (AdEERS/caAERs) for investigational agents sponsored by the CTEP IND and expeditious adverse event data sharing (21 CFR part 312.32).
3. Data and safety monitoring oversight for patients on all active trials, to include but not limited to:
   A. Reporting and monitoring safety on all trials enrolling patients at their site.
   B. Establish an internal committee to monitor and oversee patient safety, protocol compliance, and outcome and response review.
   C. Collecting and analyzing data by appropriate medical, statistical, and Clinical Research Associate (CRA) staff members.
   D. Providing high-quality data management using an effective quality assurance (QA)/quality control (QC) program, including internal review and oversight of data submission.
   E. Monitoring activities to guarantee data integrity and ample auditing.
   F. Performing statistical evaluations essential for the appropriate design, conduct, and analysis of all clinical trials.
4. Procedures for assuring that ET-CTN investigators performing trials involving CTEP IND agents are active NCI-registered investigators and have completed and submitted all required investigator registration documents (Form 1572, Financial Disclosure Form, Supplemental Investigator Data Form and Curriculum Vitae).
5. Procedures to meet Office for Human Research Protections (OHRP) requirements for the protection of human subjects, including institution assurances (Federal-Wide Assurance Number), informed consent, and CIRB reviews of protocols, amendments, and adverse events.
6. Participating in an NCI-sponsored Central Institutional Review Board (CIRB).
7. Conflict of Interest policy consistent with PHS requirements for ensuring there is no reasonable expectation that the design, conduct, and/or reporting of research conducted by the ET-CTN will be biased by any conflicting financial interest of an investigator.
8. Procedures for complying with auditing requirements and responding expeditiously to any deficiencies identified during an audit.

Data Formats

1. Data compatibility plans, including data for clinical trials. Formats, analytical algorithms, computational modeling and visualizations, and other bioinformatics tools resulting from this FOA are expected to be compatible with the NIH-approved bioinformatics platforms, such as those designed and implemented by the NCI Center for Bioinformatics platforms (http://ncicb.nci.nih.gov).
2. Procedures ensuring that claims of treatment agent activity are accurate and reliable (e.g., by establishing an independent response review panel).

Protocol templates utilized by the ET-CTN should be referenced using appropriate websites such as the CTEP website, or included in the appendix.

2.II.2.F. Sub-section F: Research Pharmacy Management – 6 pages

Describe plans for investigational pharmacy operations to fulfill obligations related to investigational agents. Summarize the existing/implemented and planned policies and procedures regarding the following elements:

Policies and Procedures

1. Access to approved protocol documents, amendments, and notification of protocol activation at the site. Notification of patient enrollment to a given protocol, including notification of signed informed consent prior to agent dispensing.
2. Availability of agents when needed. Ability to order and receive agent(s) from the supplier as instructed in the clinical protocol. Procedures regarding authorized dispensing of investigational agents to eligible study subjects on approved protocols and procedures for reconciling deviations.
3. Policies and procedures related to safe transport of investigational agents within the facility or to approved satellite facilities. Proper documentation of agent transfer to another NCI-sponsored trial and/or final disposition of investigational agents.
4. Adherence to local, state, and federal regulations and laws related to investigational agents. Policies and procedures for safe and secure handling, preparation, and disposal of dangerous goods, hazardous substances, and infectious substances.
5. Procedures for assuring that the ET-CTN sites comply with CTEP requirements described in the DCTD Investigators' Handbook for storage and accounting for investigational agents [including NCI/NIH/HHS Drug Accountability Records (DAR) procedures] and comply with FDA requirements for investigational agents.
6. Procedures to ensure NCI-supplied investigational agents are prescribed only by physicians who are registered and have an active investigator registration status with the Pharmaceutical Management Branch, CTEP.
7. Written SOPs and procedures related to investigational agent management, including agent receipt, accountability, and final disposition.
8. Training of staff and written training documentation.

Infrastructure/Equipment

1. Availability of secured access storage space and storage unit(s) necessary to meet storage conditions of agent(s). Maintenance of continuous proper storage conditions of agent(s) according to supplier instructions, including validation documentation such as temperature logs or temperature recordings and access to emergency back-up power supplies. Describe how temperature is monitored and with what frequency, what notification systems are in place in the case of temperature failures, how these situations are handled upon notification, and contingency plans in place for storage unit failures.
2. Ability to store and segregate agents by protocol, strength, unit, formulation, and investigator.
3. Adequate security of agent(s) with controlled access to authorized personnel. Limited access areas for secure and safe preparation of investigational agents.
4. Accurate completion of NCI's Drug Accountability Record Form (DARF, NIH-2564) as the primary record of all transactions related to the investigational agent(s).
5. Access to appropriate primary containment equipment, personal protective equipment, and safety equipment.

Inter-institutional pharmacy exchange and secondary distribution of investigational drugs are NOT permitted.

2.II.2.G. Sub-section G: Career Development and Mentored Training of Junior Investigators – 6 pages

A description of career development and mentored training in experimental therapeutics education and training for junior investigators (less than 7 years post oncology fellowship training) is required in this section. The proposed activities should include adequate mentorship and/or training for new and junior investigators that provides opportunities for the trainees to lead clinical trials and participate in future ET-CTN activities and/or initiatives. Training should provide opportunities to enhance skills in conducting clinical trials, skills in molecular pharmacology, and learn principles of clinical development of experimental therapeutics. Translational research ("bench-to- bedside" and "bedside-to-bench") should be an integral part of these activities. Define and career development and mentored training activities in experimental therapeutics program for Junior Investigators.

The development of junior faculty through mentorships expected to include such activities as:

1. Conducting experimental therapeutics education and training for junior investigators.
2. Mentoring and/or training programs for new and junior investigators.
3. Providing opportunities for junior investigators to lead clinical trials, as well as participate in experimental therapeutic development activities and/or initiatives.
4. Providing opportunities to enhance skill in and teach principles of experimental therapeutics.
5. Integrating translational science (bench-to-bedside and bedside-to-bench) into the training/mentoring.

Describe any relevant activities and opportunities that will be available to junior investigators in the environment of the proposed ET-CTN site:

1. Developing concepts for clinical trials to be proposed in the Career Development LOI.
2. Including junior investigators as clinical trial study chairs.
3. Providing protected time to junior faculties to perform clinical research.
4. Plans for junior investigators to attend national or international meetings relevant to experimental therapeutics.
5. Participation of junior investigators in scientific committees.
6. Available seminar series relevant to clinical experimental therapeutics, journal clubs, etc.
7. Available NIH individual education training grants.
8. Relevant trainings that will be available to junior investigators (e.g., training in regulatory requirements for drugs and devices, imaging, biomarker development).
9. Opportunities for post-doctoral training of junior investigators in experimental therapeutics.
10. Opportunities for junior investigators to work towards additional degrees (e.g., graduate level training in pharmacology).

2.III. Additional Information

2.III.1. Protection of Human Subjects

Applicants should consult the PHS 398 Application Guide regarding general instructions on what types of information should be included in the application regarding human subjects research, including the

protection of human subjects. For example, each ET-CTN application must address the inclusion of women and minorities and inclusion of children in its clinical research as required per NIH/NCI Policy.

Information on the targeted/planned enrollment table for minorities and members of both genders (as well as children, if applicable), should be based on accrual summarized across all diseases (cancer types) for the planned project period in the competing new application (Type 1), not on a study or disease-specific basis.

In addition to standard items indicated in the PHS 398 Application Guide, include in this Section SOPs and policies of the proposed ET-CTN related to study monitoring, data monitoring, and conflict of interest issues.

> Information on the policies for inclusion of women and minorities is available at:
> http://grants.nih.gov/grants/funding/women_min/women_min.htm
> http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html
> http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm
>
> Information on the policies for inclusion of children is available at:
> http://grants.nih.gov/grants/funding/children/children.htm
> http://www.nih.gov/grants/guide/notice-files/not98-024.html

NIH policy requires that children (i.e., individuals under 21 years of age) must be included in all human subjects research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them as described at: http://grants.nih.gov/grants/funding/children/children.htm. For cancer clinical research, ET-CTN Sites conducting research in adult cancers can provide a rationale for not including children because the majority of children with cancer in the United States are already accessed by a Network devoted to pediatric cancer research, so that requiring inclusion of children in the proposed adult study would be both difficult and unnecessary (since the research question is already being addressed in children by the pediatric network) as well as potentially counterproductive since fewer children would be available for the pediatric Network study if other studies were required to recruit and include children.

2.III.2.Resource-sharing Plans

Individuals are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies [GWAS]) as provided in the PHS 398 Application Guide, with the following modifications:

All applications, regardless of the amount of direct costs requested for any one year, should address a Data Sharing Plan.

It is expected that these plans will address data compatibility. Formats, analytical algorithms, computational modeling and visualizations, and other bioinformatics tools resulting from this FOA are expected to be compatible with the NIH-approved bioinformatics platforms, such as those designed and implemented by the NCI Center for Bioinformatics platforms (http://ncicb.nci.nih.gov). The data sharing plan is also expected to address procedures ensuring that claims of treatment agent activity are accurate and reliable (e.g., by establishing an independent response review panel).

2.III.3. Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in NOT-OD-10-115. **Note:** Because applications submitted in response to the Request for Applications (RFAs)/Funding Opportunity Announcements (FOAs) for the ET-CTN have only one due date, applicants may submit materials per the exceptions list in NOT-OD-10-115 using the specified page limits (see: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-115.html).

2.III.3.A. Just-in-Time Information

The following material must be submitted prior to the award of the Cooperative Agreement for the ET-CTN Sites. Several elements are not required at the time of submission. Rather, Just-in-Time information is requested by NIH staff later in the review cycle to ensure that it is up-to-date. Just-In-Time information is required to be submitted electronically through eRA Commons. See: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-101.html.

The following information is eligible for JIT submission:

2.III.3.A.1. Other Support for Key Personnel

Provide active support information for all individuals designated in an application as senior/key personnel—those devoting measurable effort to a project. Other support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards. Training awards, prizes or gifts are excluded. Sample format pages are available at: http://grants.nih.gov/grants/funding/phs398/othersupport.doc and http://grants.nih.gov/grants/funding/phs398/othersupport.pdf, however, there is no specific form provided to report on "Current Other Support." Effort devoted to projects must be measured in person-months. For all senior/key personnel, provide details on how you would adjust any budgetary, scientific, or effort overlap if this application is funded.

2.III.3.A.2. Training on Human Subjects Protection for Key Personnel

As part of Just-In-Time information, the LAO should submit a roster of Key Personnel and indicate the type of training program on human subject protections completed by each person listed. The NIH policy on Human Subject Protections is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

2.III.3.A.3. Provision of Funds to Member Institution/Sites for Accrual

If the applicant plans to provide funds to member institutions/sites for patient accruals via per-accrual reimbursement mechanisms (e.g., purchased service agreements or subcontracts), the following information must be provided as Just-In-Time information by a scheduled date to be specified by NCI/DCTD:

For the upcoming budget period:(1) the estimated number of per patient accruals by category (screening, intervention, and biospecimen accruals) by major disease area and within each disease area by trial led by the LAO; (2) the estimated number of per patient accruals by category (screening, intervention, and biospecimen accruals) by major disease area for trials that will not be led by the LAO;

and (3) the estimated total costs (direct and indirect) that the LAO anticipates providing to Integrated Components and AOs, with corresponding NCI institution codes, via this award.

2.III.3.A.4. Data and Safety Monitoring Committee/Plans and Updates

The LAO and LPO should have a Data and Safety and Monitoring Plan for early phase experimental therapeutic ET-CTN trials that complies with the "NCI Data and Safety Monitoring Guidelines" (http://www.cancer.gov/clinicaltrials/learningabout/patientsafety/dsm-guidelines/page3). In addition, the LAO must have Data and Safety Monitoring plans for all other Integrated Component and AO sites and LPO studies (e.g., phase 1 and phase 2 studies, pilot studies, etc.) that comply with the NIH policy for data and safety monitoring, posted on the NIH website at: http://grants.nih.gov/grants/guide/notice-files/not98-084.html, with additional description at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html.

LPOs conducting randomized phase 2 trials must form a Data Safety Monitoring Committee per the above referenced policies. **Note: If the NCI should decide to form a centralized Data and Safety Monitoring Board (DSMB) for randomized phase 2 studies conducted by the ET-CTN, all ET-CTN Sites will be required to utilize the centralized ET-CTN DSMB.**

These policies/plans should be provided in the research application; however, prior to funding of an award, all Data and Safety Monitoring plans and Committees need to be reviewed and approved by NCI/DCTD program staff prior to funding of an award to ensure that they are in compliance with NCI/NIH regulations.

2.IV. Description of Review Process and Review Criteria for New and Competing Applications

2.IV.1. General Information

2.IV.1.A. Role of Peer Review and Review Policies

All applications for the key components of the ET-CTN are submitted and reviewed in the same award cycle. The role of peer review is to assess the scientific and technical merit of each key component of the ET-CTN relative to their ability to promote excellence in the conduct of clinical treatment and imaging studies that may lead to a reduction in the incidence of morbidity and mortality attributable to cancer. The focus of the review is on the ability of each key component of the ET-CTN to help develop, implement, and conduct meritorious clinical trials. All applications will be reviewed based on individual review criteria categories for each of the key components of the ET-CTN which include an assessment of the application's strength to contribute to the Network as a whole. In particular, applications for the ET-CTN will be reviewed not only for their overall research strategy and scientific impact, but also on their contributions to the science of and accrual to clinical trials conducted across the entire ET-CTN and the strength of their collaborations with other ET-CTN key components and other NCI-sponsored programs and investigators.

The NCI Scientific Review Officer (SRO) serves as the Designated Federal Official (DFO) with legal responsibility for managing the review and ensuring that the review is conducted according to relevant laws, regulations, policies, and established NIH and NCI policies and procedures. The SRO provides guidance and direction with respect to review policies, procedures and criteria; the functions of the NCI staff; conflict of interest policies; implications of the Privacy Act; the need for confidentiality of the proceedings; the necessity of addressing gender, minority, and children representation in clinical study populations; and other policy and logistical matters. During the review, the ET-CTN Director serves as a

resource, as needed, concerning the history and development of the ET-CTN and other relevant programmatic matters.

1. The NCI is committed to the conduct of impartial, high-quality peer review of grant applications submitted by the scientific community and to the maintenance of an objective review process.
2. The Division of Extramural Activities (DEA), NCI, which is responsible for managing the peer review of the ET-CTN applications, is organizationally independent from the NCI extramural program units. The DEA has responsibility for and autonomy in the conduct of review activities.
3. The conduct of peer review of ET-CTN applications shall be in all particulars consistent with, and subject to, applicable NIH and PHS peer review practices and policies.
4. NCI SROs are responsible for managing the scientific and technical review of the ET-CTN applications, including the selection of reviewers; management of Special Emphasis Panels (SEPs); and the documentation of review panel findings and recommendations.
5. The responsibility for communications between the applicant and NCI staff changes during the various phases of the application process. Prior to submission of the application, NCI/DCTD staff members are the appropriate contact. From submission of the application until the peer review has been completed, all contacts should be made through the SRO.
6. Following the peer review, NCI/DCTD staff members again become the contact for communications with the applicant.
7. Efforts are made to avoid both real and apparent conflicts of interest in review of the ET-CTN applications. In addition, the confidentiality of both review materials and reviewer deliberations is maintained. Direct contact between applicants and reviewers is prohibited. Instead, any questions or concerns should be brought to the attention of appropriate NCI staff as indicated above.
8. To maintain the focus of the peer review process on scientific merit, previous and current pay lines and funding policies are not discussed and are not relevant.

2.IV.1.B. Application Receipt and Referral Process

The ET-CTN applications are received and processed initially by the NIH Center for Scientific Review (CSR) and are assigned to NCI. The NCI referral office subsequently assigns the application to the Cancer Therapy Evaluation Program in NCI/DCTD. Finally, the Division of Extramural Activities review the ET-CTN applications and recruit appropriate reviewers for the Special Emphasis Panel(s) or SEP(s), as needed, to review the ET-CTN applications, depending on the expertise needed. **In general, the reviewers will need to assess the value of the applications from the perspective of how the application contributes to the clinical research of the ET-CTN as a whole.**

2.IV.1.C. Application Administrative Review

Upon receipt, the SRO reviews the application for conformance to applicable NIH and PHS policies and Program Staff accepts the application based upon responsiveness to the ET-CTN Guidelines. If there are extensive deficiencies in the structure, organization, or format of the application or the application fails to address required NIH policies in ways that cannot be resolved quickly, the application will be returned to the applicant without further consideration.

2.IV.1.D. Review Format

All review panels are constituted as SEPs. The SEP reviewers evaluate and score general and relevant specific review criteria as appropriate for applications for each key component of the ET-CTN and then assign an overall impact/priority score to the entire application.

The SEP membership will include:

1. Senior investigators, many of whom have experience with early phase experimental therapeutics.
2. Clinical trial networks and organizations in oncology and who can view the proposed science from an overall perspective.
3. Specialists for specific scientific areas (e.g., statistics, data management, translational science including biospecimens, radiotherapy, imaging).

In organizing the review panel membership, conflicts of interest, either real or apparent, will be managed according to NIH policy.

The SRO will provide an introductory orientation on NIH and NCI review policies and procedures and administrative and logistic matters relating to the review. Senior NCI/DCTD staff will be available to provide clarification upon the SRO's request during orientation for reviewers of the ET-CTN.

The reviewers will evaluate and rate each application for the general and FOA-specific review criteria as appropriate. **The reviewers will need to assess the value of each application as to its potential to contribute to the clinical research of the ET-CTN as a whole. The review panel will then assign the final overall impact/priority score to the each application.**

NCI SROs prepare the summary statement using the minimally edited reviewers' comments as well as summaries of the discussion.

2.IV.1.E. Selection of Reviewers

The size and composition of the SEP will be determined by the particular details of the applications to be reviewed. It is the responsibility of the SRO to make these determinations based upon thorough understanding of the work proposed in the applications and consultation with NCI/DCTD staff and other NCI review staff, as appropriate. The review panel members are recruited based on the scientific areas, approaches, and administrative expertise needed to evaluate the applications. It is anticipated that the SEP convened for ET-CTN reviews in the future will, therefore, change every review cycle.

Since clinical trials are based on outcome endpoints for human subjects, the SEP will also include one or more patient/consumer advocates in the review. These individuals, who have full reviewers' rights, often address clinical or population-based study issues related to protection, recruitment and retention of human subjects in the proposed research that is essential for the success of the ET-CTN.

In identifying prospective qualified reviewers, the SRO takes full advantage of many available resources, including existing databases of experienced reviewers, lists of grantees and contractors, and consultation with recognized authorities in the scientific community. The SEP roster will be available on the NIH website approximately 30 days before the review meeting, but is subject to change. All review-related communications with actual or potential reviewers are through the SRO.

The Chairperson of the review panel will generally be a senior investigator experienced in the review of complex multidisciplinary multi-institutional clinical trials, especially late phase clinical trials, and generally knowledgeable about clinical trial networks/organizations as well as the scientific areas to be reviewed.

2.IV.2. Review Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

The overarching goal of this FOA is to bring novel anticancer agents into early therapeutic clinical trials for cancer patients. This goal requires investigators with outstanding leadership, robust infrastructure, and a strong record of conducting clinical trials. Particularly important for the clinical development of current generations of experimental cancer therapeutics is the ability to integrate clinical trials with translational approaches and additional clinical studies, including the ability to obtain and analyze PK/PD and biomarker data in all patients enrolled on all studies. Essential for ET-CTN will be the awardees' ability to work as part of a network. In this context, the important aspects are whether the applicants have assembled a team of investigators capable of conducting state-of-the-art early phase therapeutics trials and PD-pilot studies in patients with cancer, and whether they will be able to work as a coherent research team to efficiently and expeditiously conduct early phase clinical trials.

Overall Impact

Insert program-specific introductory text. Do not insert review criteria, instructions to applicants, or review considerations in this text block. If there is nothing to note for this FOA, then the above text block should be deleted. For multi-component research applications, be sure to identify those criteria that will be considered in the overall score by clearly identifying additional review criteria and additional review considerations for each component.

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the proposed ET-CTN Site to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the ET-CTN proposed).

Scored Review Criteria-Overall

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a program that by its nature is not innovative may be essential to advance a field.

Significance

Does the proposed ET-CTN Site address an important problem or a critical barrier to progress in the field? If the aims of the proposed ET-CTN Site are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Specific for this FOA:

Will the ET-CTN site, as proposed, be able to introduce appropriate novel anticancer agents into oncology clinical trials in a timely, safe, and efficient manner?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the proposed ET-CTN Site? If Early Stage Investigators or New Investigators, or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Specific for this FOA:

Does the project have adequate biostatistical expertise to conduct and analyze complex clinical and molecular data? How complete and comprehensive is the expertise of the PD(s)/PI(s) and the entire team of investigators assembled by the applicant(s) in terms of their ability to conduct state-of-the-art early experimental therapeutics studies in patients with cancer? How well do the research experience and qualifications of the PD(s)/PI(s) correspond to the need for multi-disciplinary capabilities (e.g., in medical oncology, radiation oncology, imaging, surgery) and across a broad range of cancer types?

Will these investigators be able to work as a coherent research team to efficiently and expeditiously conduct early phase clinical trials?

Do the PD(s)/PI(s) demonstrate the ability to facilitate collaborations between ET-CTN investigators and other clinical/translational science investigators?

Do the PD(s)/PI(s) have sustained, high-level participation in the scientific leadership of early experimental therapeutics (e.g., serving as scientific committee or protocol/trial study chairs, contributing new trial ideas including participating in LOI development, co-authoring publications on clinical trials research)?

What is the ability of the PD(s)/PI(s) to contribute in a meaningful way to the development of clinical trials in rare cancers?

How capable are the PD(s)/PI(s) of providing meaningful contributions to translational research, PK/PD, biomarker assays, and molecular characterization integral to or integrated into the ET-CTN clinical trials?

Do the PD(s)/PI(s) have adequate and appropriate experience in administering clinical trial research, including organization and management of the infrastructure required for patient recruitment/accrual, data collection, data reporting, and safety monitoring for patients enrolled on clinical trials?

Are the other key personnel appropriately trained and well suited to carry out the work associated with early clinical trials?

Is there sufficient and appropriately experienced support personnel available for the proposed ET-CTN Site with the skills needed to develop, implement, and analyze early phase experimental therapeutic clinical trials?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of

research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Specific for this FOA:
Do the applicants propose novel or improved ways and/or methods to enhance or better conduct early clinical trials?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Specific for this FOA:
Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the ET-CTN site?

How strong are the overall approaches proposed for individual components of the ET-CTN?

Do the research plans demonstrate an appropriate understanding of research opportunities in drug development and of the methodologies available to exploit these opportunities?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

2.IV.3. Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Relevant Capabilities and Past Performance
How strong are the applicants' expertise and experience in early phase clinical trials for patients with cancer? Specifically, how adequate is this experience in terms of collection, management, and analysis of data from single institution or multi-institution clinical trials? What is the level of applicants' experience in performing independent response auditing?

How productive were the applicants in terms of the timeliness of the development, implementation, and completion of recently conducted early phase clinical trials?

How accomplished are the applicants in terms of their research contributions (documented by peer-reviewed publications) to multi-institutional early phase experimental therapeutic clinical trials and dissemination of the results of such research?

Leadership, Governance, and Site Organization
To what extent are the proposed leadership and governance structure, decision-making processes, and interactions among key investigators optimal for designing and conduct of multi-disciplinary, multi-institutional clinical trials in a range of cancer types and special populations?

For applications designating multiple PD/PIs, is the leadership approach, including the designated roles, responsibilities, governance, and organizational structure consistent with the aims of the project and the expertise of each of the PD/PIs?

How well are defined the plans for an appropriate governance structure to coordinate activities related to the ET-CTN across the various disciplines and departments at the LAO institution?

Are the proposed leadership efforts and activities reasonably distributed across such areas as patient enrollment, clinical data collection and management? Are these efforts optimally balancing the various disciplines and the roles of clinical departments involved in the clinical trials at the proposed ET-CTN Site)? Are these plans in line with the proposed workload and anticipated accrual to clinical trials to ensure/enhance participation in ET-CTN trials by various disciplines at the LAO?

Is the staffing plan appropriate to ensure the efficient governance of the proposed ET-CTN site?

Are the organizational plans for the LAO sufficient and optimal to ensure the LAO's ability to develop, propose, implement, and monitor ET-CTN clinical trials?

How appropriate is the proposed organization to ensure monitoring the performance of the affiliated clinical sites (AOs) in an ongoing manner?

How adequate is the ET-CTN organization in terms of supporting other aspects of early clinical trials and related activities? How well is the organization of the proposed ET-CTN site matched to its leadership (especially for applications designating multiple PD/PIs)?

Team Science for Project Development
How strong is the potential of the applicants for team science approaches to developing and implementing ET-CTN's early phase experimental therapeutic studies?

At what level will the proposed ET-CTN Site be able to participate (and/or lead) inter- and trans-disciplinary team-based research efforts, including potential for interactions with investigators from other ET-CTN Sites, other NCI-sponsored programs, and NCI staff members?

PK/PD, Biomarker Assays, and Molecular Characterization of Patients
Are the proposed plans and capabilities for incorporating PK/PD, and pharmacogenomic endpoints into the clinical trials appropriate and sufficient?

Are the proposed plans and capabilities for incorporating molecular characterization endpoints into the clinical trials appropriate? In particular, is the scope of such efforts sufficient, given the goal to include in

these characterizations a high fraction of patients participating in clinical trials? Are the plans and capabilities for incorporating imaging endpoints into the ET-CTN's overall research program sufficient? How strong is the applicants' understanding of the potential of imaging studies to aid drug development?

Coordination of Clinical Trials and Associated Activities

Protocol Development and Clinical Trial Execution. How appropriate are the overall coordination efforts for ensuring timely development of clinical trial protocols and clinical trial execution? Are the measures planned to maintain the proficiency of institution personnel in the management of early phase experimental therapeutic clinical trials clearly defined and sufficient? How appropriate and adequate are the mechanisms of periodic review of QA/QC, data management procedures, and safety monitoring? Will the proposed ET-CTN site have appropriate statistical expertise and support? How appropriate are study designs for early phase experimental therapeutic clinical trials that the applicants used previously? How appropriate are statistical designs for early phase clinical trials proposed for the ET-CTN? Do the ET-CTN Sites have sufficient statistical support and utilize appropriate statistical design approaches for early experimental therapeutic clinical trials?

Correlative Studies. Does the applicant demonstrate the ability to obtain, process, and store high-quality specimens? Does the applicant demonstrate the ability to analyze and report on specimens from PK/PD and/or molecular characterization studies?

Data Analysis, Quality Assurance/Quality Control, and Reporting. Are the applicants' capabilities for the analyses of data from multi-institutional clinical trials sufficient for the expected scale of activities? Does the application demonstrate adequate procedures to monitor and analyze the data and assure the safety of patients/participants? Are the QA/QC procedures adequate and sufficient to ensure the accuracy, integrity, and security of clinical trials data? Does the application demonstrate adequate procedures to review, analyze, and report data on serious and expedited adverse events? Are procedures for reporting of data from early phase clinical trials to CTEP using CTMS electronic data capture system sufficiently timely and reliable? Are all the critical needs for the required regulatory compliance adequately addressed?

Research Pharmacy Management. Are the resources, facilities, and equipment for research pharmacy management (including appropriate secure storage units) sufficient and in line with all applicable regulations? Do the proposed plans adequately address the needs for proper procedures for handling of experimental agents and maintaining all associated documentation? How complete is evidence that Research Pharmacy in the proposed ET-CTN Site will (a) adhere to all applicable regulations with regard to investigational agent handling, (including transport and disposal); and (b) will maintain proper documentation and record keeping, transport, etc.?

Career Development and Mentored Training of Junior Investigators. Is there adequate institutional commitment to mentorship, training, and support of junior investigators in experimental therapeutics? What are the overall quality and expected effectiveness of the mentoring plans? How well do the plans incorporate the opportunities for junior investigators to learn the principles of early clinical development of experimental therapeutics and participate (or lead) relevant clinical trials, participate in scientific committees, etc.? How sufficient is the intended training in translational research? How valuable are for the ET-CTN goals other training and educational opportunities available to junior investigators?

Protections for Human Subjects. For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Inclusion of Women, Minorities, and Children. When the proposed ET-CTN Site involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the Human Subjects Protection and Inclusion Guidelines.

Vertebrate Animals. The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards. Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

2.IV.3.D. Additional Review Considerations

As applicable for the ET-CTN Site proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

How well are the applicants' budget projections aligned with the program objectives and proposed scale of operation? Are the funding allocations for PK/PD studies reasonable, appropriate, and not duplicative of other institutional funding?

2. IV.4. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s), convened by the NCI in accordance with NIH peer review policy and procedures, using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

1. May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
2. Will receive a written critique.

Appeals of initial peer review will not be accepted for applications submitted in response to this FOA.

Applications will be assigned to the NCI and will compete for available funds with all other recommended applications submitted in response to this FOA. Following initial peer review, recommended applications will receive a second level of review by the National Cancer Advisory Board. The following will be considered in making funding decisions:

1. Scientific and technical merit of the proposed project as determined by scientific peer review.
2. Availability of funds.
3. Relevance of the proposed project to program priorities.
4. The adequacy of the resources-sharing plan

Reviewers will score an application as presented in its entirety, and Scientific Review Officers will be responsible for enforcing compliance with the policy. Under no circumstance may reviewers or the SEP as a whole:

1. Modify their final overall impact scores for an application based on the assumption that a portion of the work proposed and/or budget requested will be deleted or modified according to the recommendations.
2. Recommend reducing the complexity of an application and score on the basis of the more meritorious components.
3. Provide a numerical overall impact score for an application if the SEP votes that a portion of the application be Not Recommended for Further Consideration (NRFC). However, a SEP may vote to streamline a component of a multi-component application or deem a component

Unsatisfactory, and vote a numerical overall impact score for the entire application, taking that component into consideration.

2. IV.5. Review Summary Statement

The summary statement is the official record of the review of the application. The summary statement includes administrative information about the application, the final overall impact/priority score if the application was discussed, codes for the committee's determination of the adequacy of protections for human subjects and animal welfare (if applicable) and several narrative sections conveying the opinions and recommendations of the reviewers assigned to the application. The summary statement for applications discussed during the review meeting will include a Resume and Summary of Discussion, an Overall Critique section summarizing the strengths and weaknesses of the Overall Program, summary paragraphs listing the strengths and weaknesses and the final impact score/rating of each scored review criteria category, and resumes for human subjects, vertebrate animals (if applicable) and other additional review criteria, which are prepared by the SRO.

The summary statement will also contain individual reviewers' criteria category scores along with the essentially unedited critiques. Applicants should note that some reviewers may not have updated their critiques after the review meeting to reflect their final opinions after the discussion. However, the overall Resume and Summary of Discussion, the Overall Critique section, and the summary paragraphs prepared by the SRO will reflect the final opinions of the review committee.

For applications that are not discussed during the meeting, the summary statement may not include an Overall Critique section, but it will include the individual criteria category scores along with the essentially unedited critiques and other components of the application.

The SRO prepares the summary statements as soon as possible after each review meeting. Each summary statement is released as soon as it is completed. Depending on the number of applications that were reviewed in each SEP, summary statements are usually completed within 6 weeks after the review meeting. The PI(s) can access the summary statement through the NIH eRA Commons (http://commons.era.nih.gov) after it has been finalized and released by the SRO. The summary statement will be transmitted to the National Cancer Advisory Board (NCAB) for second level peer review, to the NCI official file and to the appropriate NCI/DCTD staff.

2. IV.6. Awards

The award and administration of key components of the ET-CTN are subject to the same policies and procedures as other research grants. These policies and cost principles are set forth in the current PHS Grants Policy Statement, other NIH and NCI issuances and Federal legislation and regulations.

Following review by the NCAB, scored applications are considered for funding by the NCI.NCI/DCTD program staff may administratively delete funding or reduce the duration of support for components of the key component that are judged by peer review to be less meritorious and/or nonessential to the conduct of the component.

2. IV.7. Questions on Review Process

Questions related to the review of all ET-CTN key components review may be directed to:

Referral Officer

Division of Extramural Activities (DEA)
National Cancer Institute (NCI)
6116 Executive Boulevard, Room 8041, MSC 8329
Bethesda, MD 20892 (for U.S. Postal Service express or regular mail)
Rockville, MD 20852 (for non-USPS delivery)
Telephone: (301) 496-3428
FAX: (301) 402- 0275
Email: ncirefof@dea.nci.nih.gov

Part 3: Guidelines for Submission of Continuing Applications (Annual Progress Reports)

3.I. Pre-Application Consultation and Application Submission Instructions

The following sections include instructions on the types of information that should be included in the non-competing continuation applications (Type 5 Applications) submitted by the ET-CTN, i.e., the Annual Progress Reports. Applicants should consult the PHS 2590 at: http://grants.nih.gov/grants/funding/2590/2590.htm for up-to-date information on NIH requirements for completing the annual Progress Report or Type 5 Application. The Annual Progress Report (Type 5 Application) is required for every year of award, including the year in which a competing continuation application (Type 2 Application) may be submitted.

The Progress Report should contain the basic information needed to allow the responsible NCI ET-CTN Program Director to monitor the progress and performance of all ET-CTN Sites.

The submission procedures for non-competing continuation applications are described below.

SENDING A NON-COMPETING APPLICATION TO THE NIH:
Two (2) months before the start of the budget period, submit the original application, signed by the PI(s) and the authorized business official, and one copy of the application to the address below, according to the instructions in the PHS 2590.

Division of Extramural Activities Support, OER
National Institutes of Health
6705 Rockledge Drive, Room 2207, MSC 7987
Bethesda, MD 20892-7987 (for U.S. Postal Service [USPS] Express or Regular mail)
Bethesda, MD 20817 (for Express/courier Non-USPS Service)
Phone: 301-594-6584

NOTE: All applications and other deliveries must be delivered either via courier or via USPS. Applications delivered by individuals will not be accepted. C.O.D. applications will not be accepted. This policy does not apply to courier deliveries (e.g., FedEx, DHL, etc.).

The procedures for non-competing continuation applications for all key components of the ET-CTN are the same. The information provided in the application or annual report, however, should be focused on the specific activities of these entities (e.g., collection, transfer, and assessment of data collected or therapy delivered on a clinical trial and/or participation in trials rather than on the development of a specific scientific agenda and series of clinical trials).

3.II. Non-Competing Continuation Applications Format and Budget Requests

The information included in a non-competing continuation application (also called an annual progress reports or Type 5 Application) should be provided in formats similar to the ones presented in this Part of the Guidelines and should follow the requirements of the PHS2590 available at: http://grants.nih.gov/grants/funding/2590/2590.htm.

Providing the information in a standard format will allow the ET-CTN Director and Co-Program Directors/Project Scientists to evaluate the progress of the key components more easily and to identify

areas that need attention. The instructions on the following pages cover application formats for the ET-CTN. The non-competing continuation application must specify the 12-month period for which data are being reported, and this same 12-month period should be used for all information presented.

It is anticipated that additional instructions/modification as to what information should be included in the annual progress report may be given to awardees by the ET-CTN Director prior to submission of the first annual progress report, especially with respect to streamlining the report.

3.III. Applications for all Key Components of the ET-CTN

3. III.1. Research Plan (Annual Progress Report – Type 5 Application)

The Research Plan for each Type 5 application should follow the requirements of the PHS2590.In all cases, brief and concise descriptions in the research plan of annual progress are encouraged. **Accrual and clinical trial performance described below apply to the annual progress reports for the ET-CTN Awardees.**

In addition to standard information, provide in this section documentation of important capabilities and available resources for specific functional components of the ET-CTN LAO. Relevant information may be provided in tabular form as listed below. Applicants are strongly encouraged to use, as appropriate, table templates provided in Part 4 - Appendices (Appendices Tables).

Table 1.	**Leadership Staffing**
Table 2.	**Completed and Ongoing Phase 1 and Phase 2 Clinical Trials**
	List Phase I clinical trials that have been completed during the last 5 years and of any ongoing clinical trials for which significant research findings are available. Include first-in-human studies and trials that determined dose and schedule for both single agents and investigational agent combinations. Phase II trial examples may be provided. A table is recommended that enumerates total actual accrual by year for each clinical trial described. (See table in Appendix 4 of the ET-CTN Guidelines)
Table 3.	**Other Scientific Achievements for Clinical Trials**
Table 4.	**List of PK/PD Assays Performed during Conduct of Early Phase Clinical Trials**
	List in a Summary Table all PK and PD research contributions and accomplishments for PK and PD studies associated with early phase clinical trials.
Table 5.	**Summary Accrual for Screened and Treated Patients on All Early Experimental Therapeutic Clinical Trials**
Table 6.	**Summary of Letters of Intent Submitted and Approved, and Protocols Submitted**
	A listing of clinical trial protocol development activities during the last 5 years, including relevant dates and milestones for LOIs submitted, clinical trial protocols submitted, and clinical trials activated, with timelines for specific steps in the clinical trial protocol development process including accrual rate projected and achieved, total accrual, study duration and use of novel trial designs, such as the accelerated titration design.
Table 7.	**Inclusion Enrollment Report**
	Annual accrual to early phase clinical trials by gender and ethnicity/race composition

	should be described in the PHS 398 Inclusion Enrollment Report form (http://grants.nih.gov/grants/funding/phs398/enrollmentreport.pdf). Trials should be grouped by phase of study.
Table 8.	**Operational Timelines for Activation of Clinical Trial Proposals**
	List timelines for the LAO and any AOs (if applicable).
Table 9.	**Patient Accrual for Individual Clinical Trials**
	List actual timelines for specific steps in the clinical trial protocol development process, including accrual rate projected and achieved, total accrual, and study duration.
Table 10.	**Summary of Biomarker and Correlative Studies**
	A description of biomarker assays and other correlative laboratory studies performed on patient tissue during the previous five years, including surgical or image-guided biopsies. A tabular format is preferred and should include the trial number, title, correlative goals and objectives, a list of the planned integral and integrated biomarkers explored during the conduct of the study, patient concurrence with biopsy procedure, informed consent opt-in/opt-out, percent success rate, publication citation, etc.
Table 11.	**List of Procedures and Policies**
	List the relevant Standard Operating Procedures (SOPs) and LAO policies including, but not limited to: specimen acquisition and handling; tumor banking procedures and policy; Institutional Review Board (IRB) policies; Human Subjects Research Protections (HSRP) policies; safety; and pharmacovigilance procedures and policies, assay validation procedures, etc.

Clinical Trial Performance
LAOs should also summarize the timeliness of AdEERS reports submission, the date of the last audit for institutional members (or Lead Academic Participating Site), compliance with specimen submission, etc. in the annual report.

Operational Timelines for Activation of Clinical Trial Proposals (Table 8)
The annual progress report should list protocol development activities during the current funding period for ET-CTN Sites, in terms of submitted and approved Letters of Intent (LOIs), submitted and approved protocols, activated and completed trials with associated OEWG timelines.

Progress & Summary of Research Achievements of ET-CTN Site (Table 2 and 3)
The annual progress report for the ET-CTN Site should report on the site's progress regarding the goals and activities outlined in the research plan of the corresponding Type 1 application. This should include information on how the ET-CTN Site has contributed to the goals of the ET-CTN, with emphasis accomplishments during the current funding period.

The application should provide a brief, narrative description of the contributions of the ET-CTN Site to ET-CTN clinical trials and research goals and other ET-CTN activities and initiatives, including important collaborations, during the current funding period. This summary narrative should be adequate to convey the important facets of the activity and any significant findings (e.g., patients accrued, open dose level, important toxicities observed, PK findings, anti-tumor activity observed, scientific leadership on new trials, translational science advances, etc.).

The annual progress report should list the titles and complete references of all publications not previously reported. This includes manuscripts submitted or accepted for publication. Only those publications resulting directly from activities of the ET-CTN should be reported.

The NIH Public Access Policy requires scientists to submit final peer-reviewed manuscripts that result from direct costs funded by NIH, and that are accepted for publication on or after April 7, 2008, to PubMed Central. Compliance with the NIH Public Access Policy is a legal requirement (Consolidated Appropriations Act of 2008, Public Law 110-161, Division G, Title II, Section 218) and a term and condition of an award. If a grantee has failed to materially comply with the terms and conditions of award, NIH may suspend the grant, pending corrective action, or may terminate the grant for cause (per 45 CFR 74.61, 74.62, and 92.43).

Ensure the following:

1. **If the manuscript(s) were accepted for publication on or after April 7, 2008, please enter these documents into PubMed Central as soon as possible.** Information on how to submit manuscripts can be found at: http://publicaccess.nih.gov/submit_process.htm.
2. You can confirm compliance by including the PubMed Central reference number (PMCID) in the list of publications. Please see the Frequently Asked Question (FAQ) if you have questions about how to use PMCIDs, or this FAQ if the PMCID has not been assigned yet.

You should include the PMCID when citing these papers in any subsequent report. Please see: Guide Notice NOT-OD-08-119 for more information and alternatives.

If you have any questions about the Policy, please check the NIH Public Access Website or send a note to PublicAccess@nih.gov.

Key Personnel and Training on Human Subject Protections for New Key Personnel
The ET-CTN Site should submit a list of key personnel (Table 1), highlighting any changes. In addition, the ET-CTN site should indicate the type of training course/program on human subject protections completed by each new key personnel member.

3.III.2. Budget (Annual Progress Report – Type 5 Application)

3.III.2.A. General Budget Information

The budget included in the non-competing application should be similar to that provided in the new application, except it is limited to the upcoming 12-month funding period.

3.III.2.B. Non-Competing Budget Adjustments

General comments: Out-year budget commitments, as reflected in each Notice of Grant Award, are based upon the funding level for the competing year; however, funding levels can be increased or reduced because of increments or decrements in performance on the part of the ET-CTN awardee or a change in the funds available to the government for distribution.

Requests for the adjustments are initiated by the ET-CTN Site, and are based on such factors as increased or decreased level of activity at an institution. The effect of any such adjustment will be reflected in revised out-year commitments. Authority to effect an adjustment rests with NCI Grants

Management Officer in the NCI Office of Grants Administration (OGA) on the recommendation of the ET-CTN Director. Funding adjustments are facilitated by the NCI/DCTD Senior Program Specialist.

Type 5 Applications are due at the NCI eight (8) weeks prior to the award date, so sufficient time should be allotted to permit timely receipt of applications in line with any request for redistribution or carryover. In connection with this time-line, it should be noted that OGA generally requires a formal, updated budget when changes of more than 25 per cent are requested.

3.III.2.C. Budget Adjustments by NCI/DCTD for ET-CTN Sites

Adjustments may be made by NCI/DCTD in the funding of ET-CTN Sites at the time of a non-competing continuation award. Such adjustments provide the NCI with the ability to ensure that available funds are put to their best use. Authority to effect adjustments in funding rests with the ET-CTN Director, who works in conjunction with the NCI/DCTD Senior Program Specialist.

Budget commitments for the non-competing years are based upon the funding level for the competing year. Increases or decreases in funding for any ET-CTN Site may be made on the basis of changes in performance relative to that approved in the competing application or in the previous year. The actual monies awarded are always, of course, subject to the availability of funds. Thus, funding levels can be increased or reduced because of increments or decrements in performance on the part of the awardee, particularly with respect to funding restricted for use to cover data collection/management and biospecimen collection related to enrollment of patients on clinical trials and their follow-up and/or a change in the funds available to the government for distribution.

In particular, the ET-CTN Site will undergo assessment with possible decrement in funding after 3-years of performance based on the awardee's accrual to ET-CTN trials.

3.IV. Notification of International Involvement in ET-CTN Sites

The ET-CTN Site must alert the NCI/DCTD Senior Program Specialist and the Office of Grants Administration (OGA) when a non-competing application involves any new international (non- U.S.) component, regardless of whether the component receives federal funding under the awardee's grant. In such cases, advance clearance from the U.S. Department of State is required for each non- U.S. component prior to the start date of the award. The information required by U.S. Department of State for each foreign component/site is listed below (this information should also include all non- U.S. subcontracts).

1. Estimated annual Total Cost dollar award for the non- U.S. component
2. Name, organization, city, and country of the International (non- U.S.) Principal or Collaborating Investigator(s)
3. Biosketch and Curriculum Vitae (CV) for both the domestic PI and the international PI
4. OHRP assurance number (i.e., Federal Wide Assurance number) for the non-US component
5. Brief summary of responsibilities and activities of the foreign component.

In addition, for international sites collaborating with an ET-CTN Site on trials sponsored under the ET-CTN (regardless of whether the U.S. or Canadian organization or the international organization is leading the trial and regardless of whether any funding is being provided), U.S. Department of State clearance is required for the non-U.S. country as clinical data is being passed between the U.S./Canadian organization supported under the ET-CTN and the other country.

Part 4: Appendices

4.I. NCI/DCTD Policies for the ET-CTN (URLs to Websites)

NCI National Clinical Trials Network Program (ET-CTN) Guidelines
http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

Investigator's Handbook (A Handbook for Clinical Investigators Conducting Therapeutic Clinical Trials Supported by CTEP, DCTD, NCI)
http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

NCI-CTMB Guidelines for Monitoring of Clinical Trials for Cooperative s, CCOP Research Bases, and the Cancer Trials Support Unit (CTSU)
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm

IP Option Policy
http://ctep.cancer.gov/industryCollaborations2/default.htm#guidelines_for_collaborations
http://ctep.cancer.gov/industryCollaborations2/default.htm

Operational Efficiency Working (OEWG) Policy and Timelines
http://ctep.cancer.gov/SpotlightOn/OEWG.htm

Policy on Contract Review
http://ctep.cancer.gov/industryCollaborations2/guidelines.htm
(Under NCI Standard Protocol Language for Collaborative Agreements)

Early Stopping Guidelines for Slowly-Accruing Phase 3 Studies
http://ctep.cancer.gov/protocolDevelopment/default.htm#cde_data_pol_cdus
(Under CDE / Data policies / CDUS – Slow Accrual Guidelines for Phase 3 Trials)

Adverse Event Expedited Reporting System (AdEERS)
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Information on Common Data Elements (CDE) Approved for Use in CTEP-sponsored Clinical Trials
https://cabig.nci.nih.gov/community/concepts/caDSR/

NCI's Common Terminology Criteria for Adverse Events (CTCAE)
http://ctep.cancer.gov/reporting/ctc.html

NCI Clinical Trials Cooperative Program Guidelines for the Development, Conduct and Analysis of Clinical Trials with International Collaborating Institutions (Under Guidelines & Policies)
http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

CTEP Conflict of Interest Policy for Cooperative Phase 3 Clinical Trials (Under Guidelines and Policies)
http://ctep.cancer.gov/investigatorResources/default.htm#guidelines_policies

PART 4: Appendices

NCI Templates for Simplified Model Informed Consent Documents for ET-CTN Trials
http://ctep.cancer.gov/protocolDevelopment/default.htm#informed_consent

Guidelines for Auditing of Clinical Trials for Early Therapeutics Clinical Trials Network (ET-CTN)
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ET-CTN_Audit_Guidelines.docx

ET-CTN Code of Conduct (TO BE PROVIDED).

The National Institutes of Health (NIH) Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)
http://gwas.nih.gov/03policy2.html

Privacy and Progress in Whole Genome Sequencing
http://www.bioethics.gov/cms/sites/default/files/PrivacyProgress508.pdf.

4.II. Suggested Formats - Tables for New & Non-Competing Applications

The tables provided in this section are to assist in the documentation of important capabilities and available resources for specific functional components of the ET-CTN LAO. **Applicants are strongly encouraged to use, as appropriate, table templates.**

Current and/or relevant information in the past 5-6 years should be used in the tables unless otherwise indicated.

Provide information on key leadership staff and their role in the ET-CTN site. Add rows as needed.

Staffing Category	Member Designation	Member Name	Title	Institution	Length of Service in Position
Lead Academic Organization PI					
Integrated Component PI(s)					
Affiliated Organization PI(s)					
Lead Statistician(s)					
Pharmacy Leader(s)					
Administrative Coordination Component Leader					
Regulatory Leader					
QC/QA Leader					
Data Monitoring Leader					
Head Research Nurse(s)					
Lead Protocol Coordinator(s)					
Senior Clinical Research Associate(s)					

Template Table 2: Completed and Ongoing Phase I and Phase II Clinical Trials
MM/YYYY to MM/YYYY

Include phase 1 clinical trials that have been completed during the last 5 years and any ongoing clinical trials for which significant research findings are available. Include first-in-human studies and trials that determined dose and schedule for both single and investigational agent combinations. Phase II trial examples may be provided. Enumerate total actual accrual by year for each clinical trial described. Add rows as needed.

Cancer Site	Trial Phase	Year (publication or other)	Trial Number & Brief Title	Experimental Agent or Regimen	Primary Endpoint Result-indication	Manuscript or Abstract Reference	Incorporated into Practice Guidelines (Type Guidelines, Year)	FDA Approved Labeling Indication or other important impact (Describe)	Date Trial Activation	Date Trial Closure	Total Accrual

Template Table 3: Other Scientific Achievements for Clinical Trials
MM/YYYY to MM/YYYY

Include important achievements that were reported only in the last 5 years. Add rows as needed.

Cancer Site	Trial Phase	Year (publication)	Trial Number & Brief Title	Experimental Agent or Regimen	Secondary Endpoint or Sub-Study Result	Manuscript or Abstract Reference	Description of Importance from Secondary Endpoint or Sub-study	Date Trial Activation	Date Trial Closure	Total Accrual

Template Table 4: List of PK/PD Assays and Molecular Characterizations Performed During Conduct of Early Phase Clinical Trials
MM/YYYY to MM/YYYY

Describe all PK and PD research contributions and accomplishments for PK and PD studies associated with early phase clinical trials over the past 5 years. Add rows as needed

Cancer Site	Year of Request	Trial Phase	Trial Number & Brief Title	Brief Description of Request	# and Type Samples Provided	Date Samples Provided	Reference to Publication Resulting from Approved Request or Other Result (or Pending Publication)

Template Table 5: Summary Accrual for Screened and Treated Patients on All Early Experimental Therapeutic Clinical Trials

Describe the number of patients screened and the number of patients treated on clinical trials that were/are led by the applicant or where the applicant accrued patients to a clinical trial but was not the lead on the protocol. Include accrual only over the past 5years.
Add rows as needed. S=Screened S&T = Screened and Treatment Tx = Treatment

Study Accrual Period (MM/YYYY) to MM/YYYY)	Pilot and/or Exploratory IND Studies (Phase 0) Tx Studies			Phase 1 Tx Studies			Phase 1 Combination Tx Studies (Includes phase ½ studies)			Phase 2 Tx Studies			Phase 2 Combination Tx Studies		
	S	S&T	Total	S	S & T	Total	S	S & T	Total	S	S & T	Total	S	S & T	Total
Study Title and Protocol Number #1															
Accrual **to Trial Led** by Applicant															
Accrual **to Trial NOT Led** by Applicant															
Study Title and Protocol Number #2															
Accrual **to Trial Led** by Applicant															
Accrual **to Trial NOT Led** by Applicant															
Total	Sum of Total **column**														
Grand Total (across all studies)	(Sum of all totals in "Total" **row**)														

Template Table 6: Summary of Letters of Intent (LOI) Submitted and Approved, and Protocols Submitted
MM/YYYY to MM/YYYY

List Phase 1 clinical trial protocol development activities during the last 5 years, including relevant dates and milestones for LOIs submitted, clinical trial protocols submitted, and clinical trials activated. Add rows as needed.

	LOI Number Designation	Date Submitted	Date Approved/ Disapproved	Date Protocol Submitted	Date Protocol Approved	Date Trial Activated	Date Trial Completed	Type of Novel Trial Design
Study Title #1								
Study Title #2								
	# of LOIs	# Submitted	#Approved	# Submitted	# Approved	# Activated	# Completed	
Total (across all studies)								

Template Table 7: Inclusion Enrollment Report

For the FOA submission, submit one summary table for total accrual for each completed trial over the past 5 years. For annual progress reports, submit one table for each individual protocol reported in the annual progress report for the ET-CTN sites. Do not modify the table.

Program Director/Principal Investigator (Last, First, Middle):

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title:

Total Enrollment: **Protocol Number:**

Grant Number:

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race				
Ethnic Category	**Females**	**Males**	**Sex/Gender Unknown or Not Reported**	**Total**
Hispanic or Latino				**
Not Hispanic or Latino				
Unknown (individuals not reporting ethnicity)				
Ethnic Category: Total of All Subjects*				*
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More Than One Race				
Unknown or Not Reported				
Racial Categories: Total of All Subjects*				*

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)				
Racial Categories	**Females**	**Males**	**Sex/Gender Unknown or Not Reported**	**Total**
American Indian or Alaska Native				
Asian				
Native Hawaiian or Other Pacific Islander				
Black or African American				
White				
More Than One Race				
Unknown or Not Reported				
Racial Categories: Total of Hispanics or Latinos**				**

* These totals must agree.
** These totals must agree.

PHS 398/2590 (Rev. 06/09) Page Inclusion Enrollment Report Format Page

Template Table 8: Operational Timelines for Activation of Clinical Trial Proposals MM/YYYY to MM/YYYY

Describe operational timelines for the LAO and any AOs (if applicable) for specific steps in the clinical trial protocol development process. Include only trials open or submitted during the past 5 years. Add rows as needed.

IND Studies – Pilot and/or Exploratory IND Studies (Phase 0)

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 1

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 1 Combination

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 2

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

IND Studies – Phase 2 Combination

Cancer Site	LOI	Trial Number and Brief Title	Operational Efficiency Start Date	Date of LOI Approval	Date First Protocol Submission	Number Protocol Revisions	Date Protocol Approval	Date Study Open for Patient Accrual	Number of Days in Development	Comments

Template Table 9: Patient Accrual By Individual Clinical Trials
MM/YYYY to MM/YYYY

Describe actual timelines for specific steps in the clinical trial protocol development process, including accrual rate projected and achieved, total accrual, and study duration. Include only trials open during the past 5 years that are still accruing patients or that are temporarily closed to accrual and/or treatment. Tx = treatment Add rows as needed.

Cancer Site	Trial Phase	LOI	Trial Number & Brief Title	Date Study Open for Patient Accrual	Trial Status (Open or Temporarily Closed to Accrual and/or Tx)	Sample Size	Accrual to Date	Projected Monthly Accrual Rate	Estimated Study Closure Date (i.e. Closed to Accrual)	Anticipated Primary Completion Date	Average Actual Monthly Accrual	Average Actual Annual Accrual

Template Table 10: Summary of Biomarker and Correlative Studies
MM/YYYY to MM/YYYY

Describe biomarker assays and other correlative laboratory studies performed on patient tissue during the last 5 years, especially those that included surgical or image-guided biopsies. Add rows as needed.

Trial Number & Brief Title	Description of Study	# of Specimens			# of Specimens Requested	# of Specimens Acquired	# of Specimens Banked	# of Specimens Completed & Reported	# of Specimens Analyzed	Reference for Completed Specimens
		Baseline	During Treatment	After Treatment, Off Study or at Progression						

Template Table 11: List of Procedures and Policies

List the relevant Standard Operating Procedures and LAO policies including, but not limited to, specimen acquisition and handling; tumor banking procedures and policy; Institutional Review Board policies, Human Subject Research Protections policies, safety and pharmacovigilance procedures, assay validation, etc. Add rows as needed.

Procedure and Policies for: (specimen acquisition, CTSA, tumor banking, IRB, etc.)	Brief Title	Effective date	Issuance date	Applicable to: (institute wide, laboratory, pharmacy, etc.)	Expiration date
Standard Operating Procedures					
Policy					

4.III. Other Important NCI/NIH URLs, Federal Citations, and List of Abbreviations

A listing of important URLs (links to websites) and abbreviations referenced in the text of these Guidelines is provided below.

4.III.1. Website URLs referenced in these Guidelines

NCI Website
http://www.cancer.gov/

NCI Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)
http://biqsfp.cancer.gov/

NCI Cancer Trials Support Unit (CTSU) Website
http://www.ctsu.org

NCI Cancer Diagnosis Program's Request for an Application (RFA) on Support for Human Specimen Banking in NCI-Supported Cancer Clinical Trials
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-05-017.html

NCI Cancer Diagnosis Program's Website
http://cdp.cancer.gov/

NCI Center for Coordinating Clinical Trials
http://ccct.cancer.gov/about/overview

NCI Central IRB Website
http://www.ncicirb.org

NCI Clinical Trials and Translational Research Advisory Committee (CTAC)
http://ccct.cancer.gov/committees/ctac

NCI Clinical and Translational Research Operations Committee
http://ccct.cancer.gov/committees/ctroc

NCI CTWG Steering Committee System (Information on NCI Scientific Steering Committees)
http://transformingtrials.cancer.gov/steering/overview

NCI Clinical Trials Reporting Program (CTRP)
http://www.cancer.gov/clinicaltrials/conducting/ncictrp/main/allpages

NCI Data and Safety Monitoring guidelines
http://www.cancer.gov/clinicaltrials/learningabout/patientsafety/dsm-guidelines/page3

NCI Guide to Readers to Information on Other NCI Divisions/Branches
http://www.cancer.gov/aboutnci

Diagnostics Evaluation Branch (DRB) of the Cancer Diagnosis Program (CDP) Program for the Assessment of Clinical Cancer Tests (PACCT) – Clinical Tumor Marker Study Guidelines
http://www.cancerdiagnosis.nci.nih.gov/diagnostics/advice/guidelines.htm

Good Clinical Practice in FDA-Regulated Clinical Trials
http://www.fda.gov/oc/gcp/default.htm

Guidance Document on Inclusion of Manuscripts/Publications in Appendix Material with NIH/NCI Grant Applications
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-053.html

NIH Data-sharing Policy
http://grants.nih.gov/grants/policy/data_sharing

NIH Freedom of Information Act Office
http://www.nih.gov/icd/od/foia/index.htm

NIH Grants Policy Statement
http://grants.nih.gov/grants/policy/policy.htm

NIH Grant Policy for Program Income
http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income

NIH Guide Notice on NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research (Amendment October 2001).
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html

NIH Public Access Policy (and Manuscript Submission System)
http://publicaccess.nih.gov

NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (3/6/98)
http://www.nih.gov/grants/guide/notice-files/not98-024.html

NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research – Amended, October, 2001 (COMPLETE COPY OF UPDATED GUIDELINES)
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects – Policy Implementation
http://grants.nih.gov/grants/funding/children/children.htm

NIH Policy for Data and Safety Monitoring
http://grants.nih.gov/grants/guide/notice-files/not98-084.html

(Further) NIH Guidance on Data and Safety Monitoring for Phase 1 and Phase 2 trials
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

NIH Policies on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects – Policy Implementation
http://grants.nih.gov/grants/funding/women_min/women_min.htm

NIH Policy on Financial Conflict of Interest
http://grants.nih.gov/grants/policy/coi

PHS 398 Grant Application
http://grants.nih.gov/grants/funding/phs398/phs398.html

PHS 2590 Non-Competing Grant Progress Report
http://grants.nih.gov/grants/funding/2590/2590.htm

SF424 (R&R) Application and Electronic Submission Information
http://grants.nih.gov/grants/funding/424/index.htm

Office for Human Research Protections Website
http://www.hhs.gov/ohrp/

Required Education on the Protection of Human Subject Participants
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html

Updated Instructions Regarding Inclusion of Publications as Appendix Materials:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-077.html

4.III.2. Other Federal Citations for NIH Grants Involved in Human Subjects Research & Websites

Sharing of Model Organisms
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see: http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time, the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh-Dole Act (see the NIH Grants Policy Statement at: http://grants.nih.gov/grants/policy/nihgps_2011/nihgps_ch8.htm#_Program_Income).

All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004, receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Standards for Privacy of Individually Identifiable Health Information
This Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The

Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

Healthy People 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. The funding opportunity announcement (FOA) for this cooperative agreement is related to one or more of the priority areas. Potential applicants can obtain a copy of "Healthy People 2010" at: http://www.health.gov/healthypeople.

Authority and Regulations

This program is described in the Catalogue of Federal Domestic Assistance at: https://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency Review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service (PHS) Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at: http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American People.

Loan Repayment Program

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The Loan Repayment Program (LRP) is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40-hour week) for 2 years to the research. For further information, please see: http://www.lrp.nih.gov/.

4. III.3. Important Abbreviations Referenced in these Guidelines

ABBREVIATION	FULL TERM
AD	Associate Director, CTEP, DCTD
AdEERS	Adverse Event Expedited Reporting System
AO	Affiliated Organization
ARA	Awaiting Receipt of Application
BRB	Biometric Research Branch (in DCTD)
BRC	Biomarker Research Committee
caDSR	Cancer Data Standards Registry and Repository
CAERS	Cancer Adverse Event Reporting System
CAPA	Corrective and Preventive Action Plan
CBO	Common Budget Outline
CCCT	Coordinating Center for Clinical Trials (in NCI OD)
CCOP	Community Clinical Oncology Program (in DCP)
CDE	Common Data Elements
CDP	Cancer Diagnosis Program (in DCTD)
CDS	Clinical Data System
CDUS	Clinical Data Update System
CFR	Code of Federal Regulations
CIB	Clinical Investigations Branch (in CTEP)
CIP	Cancer Imaging Program (in DCTD)
CIRB	Central Institutional Review Board at NCI
CLIA	Clinical Laboratory Improvement Amendments
COI	Conflict of Interest
CRA	Clinical Research Associate
CRADA	Cooperative Research and Development Agreement
CrDL	Career Research and Development LOI
CSA	Clinical Supply Agreement
CSR	Center for Scientific Research (at NIH)
CTA	Clinical Trial Agreement
CTAC	Clinical Trials and Translational Research Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program (in DCTD)
CTMB	Clinical Trials Monitoring Branch (in CTEP)
CTMS	Clinical Trials Monitoring Service
CTSA	Clinical and Translational Science Award
CTSU	Cancer Trials Support Unit
CTRP	Clinical Trials Reporting Program
CTWG	Clinical Trials Working Group
CTROC	Clinical and Translational Research Operations Committee
DAR	Drug Accountability Record
DARF	Drug Accountability Record Form
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis

DEA	Division of Extramural Activities
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee (also known as Data and Safety Monitoring Board)
DR	Diagnostics Evaluation Branch (in CDP)
DSM	Data and Safety Monitoring
DSMB	Data and Safety Monitoring Board (also known as Data Monitoring Committee)
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
ET-CTN	Experimental Therapeutics-Clinical Trial Network
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FOA	Funding Opportunity Announcement
FOIA	Freedom of Information Act
FWA	FederalWide Assurance (for OHRP)
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IAM	Identity and Access Management
IB	Investigator Brochure
IDB	Investigational Drug Branch (in CTEP)
IDE	Investigational Device Exemption
IDSC	Investigational Drug Steering Committee
IND	Investigational New Drug Application
IP	Intellectual Property
IRB	Institutional Review Board
LAO	Lead Academic Organization
LOI	Letter of Intent
LPO	Lead Protocol Organization
MTA	Material Transfer Agreement
NCAB	National Cancer Advisory Board
NCI	National Cancer Institute
NCI SSC	NCI Scientific Steering Committees
NIH	National Institutes of Health
NCTN	National Clinical Trials Network
NME	New Molecular Entity
OD	Office of the Director at the NCI
OEWG	Operational Efficiency Working Group
OGA	Office of Grants Administration
OHRP	Office for Human Research Protections
OPEN	Oncology Patient Enrollment Network
ORI	Office of Research Integrity
PD	Pharmacodynamics

PHS	Public Health Service
PI	Principal Investigator
PIO	Protocol and Information Office (in CTEP)
PK	Pharmacokinetics
PMB	Pharmaceutical Management Branch (in CTEP)
PRC	Protocol Review Committee (in CTEP – also known as NIC/DCTD PRC)
PSC	Purchase Service Agreement
PTA	Project Team Application
QA/QC	Quality Assurance/Quality Control
RAB	Regulatory Affairs Branch (in CTEP)
RRP	Radiation Research Program (in DCTD)
RSS	Regulatory Support System (in CTSU)
SEP	Special Emphasis Panel
SOP	Standard Operating Procedures
SPORE	Specialized Programs of Research Excellence
SRO	Scientific Review Officer
SSC	Scientific Steering Committee
URL	Uniform Resource Locator (internet address of resource)

4.III.4. Glossary

For the purpose of this FOA, the following terms are defined as follows:

Affiliated Organization (AO): an institution collaborating with the LAO. For multiple PDs/PIs applications, an Affiliated Organization is defined as academic sites lead by the designated multiple PDs/PIs on the application, other than the LAO institution.

Biomarker: a biomarker is a validated indicator of a specific molecular disease state.

Correlative biomarker: a correlative biomarker is a validated biomarker with predictive and/or prognostic significance indicative of treatment outcome.

ET-CTN sites – the institution receiving the award under this FOA (also referred to as Lead Academic Organization, LAO) plus any entities collaborating with the LAO under subcontractual/consortium arrangements (also referred to as Affiliated Organizations, AOs) and parts of a LAO that represent the same legal entity, even if their location is different from the main location of the awardee (referred to as LAO integrated components).

Identity Access Management (IAM): an IAM is a password, user name, and role management to support access to NCI and ET-CTN systems

Integral biomarker assay: an analytically and clinically validated assay that must be performed on each subject as a condition of entry into the clinical trial. The assay must be done in a laboratory certified under Clinical Laboratory Improvement Amendment (CLIA, http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/).

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Integrated biomarker assay: this assay is done on most patients, but results will not be used for the treatment of that patient on the trial. Results usually used to validate hypotheses, and analyzed after the trial.

Lead Academic Organization (LAO): The institution receiving the award under this FOA. A LAO may have Integrated Component(s), i.e., a component of the institution receiving the award, which may be at a different location. The institution must be the same legal entity as the LAO.

Lead Protocol Organization (LPO): An LPO is the institution of the investigator who leads the clinical trial.

Project Team Applications (PTA): An application submitted in response to an NCI request that proposes projects, identifies an LPO(s) and project team members, and states capabilities.

Proof of principle studies (for target effects):Such studies are done to demonstrate that an investigational agent hits its intended target and has its expected molecular effect.